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ABSTRACT

Asthma is the most common chronic disease in children. Although early life wheezing illnesses have been suggested to play a role in the development of asthma, the influence of early childhood respiratory infections in the development of asthma is unknown. This dissertation investigates the associations between acute respiratory infections in early childhood and the risk of asthma.

In the prospective birth-cohort study called the Steps to the Healthy Development and Well-Being of Children (STEPS) Study, 923 Finnish children were followed intensively for upper and lower acute respiratory infections and the development of asthma from birth to 7 years of age. Nasal swab samples for respiratory viruses were obtained at the onset of respiratory symptoms during the first years of life. Asthma diagnoses were retrieved from medical records. Genome-wide genotyping was performed. In Study II, data from two prospective cohort studies of severe wheezing illnesses were included (n = 223).

Frequent acute respiratory infections in early childhood were associated with a higher rate of subsequent asthma. Recurrent wheezing illnesses, hospitalization for wheezing, and wheezing caused by either rhinoviruses or RSV in the first years of life were associated with an increased risk of asthma. Furthermore, both rhinovirus species A and C induced early wheezing illnesses were associated with a higher risk of asthma. Asthma risk alleles were associated with an increased risk of acute respiratory infections and viral wheezing illnesses during the first years of life.

These results contribute to the understanding of asthma pathogenesis and suggest that susceptibility to ARIs and asthma may share risk factors, or that recurrent ARIs in early childhood may predispose a child to the development of asthma. Future research should focus on interventions to modify infection-related asthma risk and the interaction between genetic and environmental asthma risk factors.

KEYWORDS: Asthma, early childhood, genetics, respiratory infections, rhinovirus

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TIIVISTELMÄ

Astma on lasten yleisin pitkäaikaissairaus. Varhaislapsuuden vinkutaudeilla on esitetty olevan merkitystä astman kehittymisessä, mutta varhaislapsuuden hengitystieinfektioiden osuutta astman puhkeamisessa tunnetaan huonosti. Tämä väitöskirja tutkii varhaislapsuuden hengitystieinfektioiden ja astman välistä yhteyttä.

Hyvän kasvun avaimet (Steps to the Healthy Development of Children) -syntymäkohorttitutkimuksessa seurattiin 923 suomalaisen lapsen äkillisiä ylä- ja alahengitystieinfektioita ja astman kehittymistä syntymästä seitsemän vuoden ikään saakka. Hengitystieoireiden alkaessa kerättiin nenätikkunäytteitä hengitystieviruksien toteamiseksi ensimmäisten ikävuosien aikana. Astmadiagnoosit kerättiin potilastiedoista. Lapsille tehtiin genomin laajuinen genotyypitys. Tutkimuksessa II käytettiin myös aineistoa kahdesta vaikeita vinkutauteja tutkineesta prospektiivisesta kohorttitutkimuksesta (n = 223).

Tiheä hengitystieinfektioiden sairastaminen varhaislapsuudessa oli yhteydessä lisääntyneeseen astmariskiin. Toistuvat vinkutaudit, sairaalahoito vinkutaudin vuoksi ja rino- tai RS-viruksen aiheuttama vinkutauti varhaislapsuudessa assosioituvat astmariskiin. Lisäksi rinovirustyyppien A ja C aiheuttamat vinkutaudit olivat yhteydessä lisääntyneeseen astmariskiin. Astmalle altistavat riskialleelit olivat yhteydessä lisääntyneeseen äkillisten hengitystieinfektioiden ja vinkutautien riskiin varhaislapsuudessa.

Tämän tutkimuksen tulokset syventävät ymmärrystä astman patogeneesistä ja osoittavat, että äkillisillä hengitystieinfektioilla ja astmalla voi olla yhteisiä riskitekijöitä, tai että varhaislapsuuden toistuvat hengitystieinfektiot altistavat astman kehittymiselle. Tulevaisuudessa tarvitaan tutkimusta geneettisten ja ympäristöriskitekijöiden välisistä yhteisvaikutuksista ja interventioista, joilla pyritään muokkaamaan infektioihin liittyvää astmariskiä.

AVAINSANAT: Astma, genetiikka, hengitystieinfektiot, rinovirus, varhaislapsuus

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Abbreviations

ARI	Acute respiratory infection
CDHR3	Cadherin related family member 3
CI	Confidence interval
DALY	Disability-adjusted life year
FEV	Forced expiratory volume
FEV1	Forced expiratory volume in one second
GSDMA	Gasdermin A
GSDMB	Gasdermin B
GWAS	Genome-wide association study
HIV	Human immunodeficiency virus
ICAM-1	Intercellular adhesion molecule 1
ICS	Inhaled corticosteroid
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IKZF2	Ikaros family zinc finger protein 2
IQR	Interquartile range
IRR	Incidence rate ratio
LD	Linkage disequilibrium
LDLR	Low density lipoprotein receptor
LRTI	Lower respiratory tract infection
NGF	Nerve growth factor
NP	Nasopharyngeal
OM	Otitis media
OR	Odds ratio
ORMDL3	ORMDL sphingolipid biosynthesis regulator 3
PAD	Primary antibody deficiency
PCR	Polymerase chain reaction
PEF	Peak expiratory flow
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus

RV	Rhinovirus
SNP	Single nucleotide polymorphism
STEPS	Steps to the Healthy Development and Well-Being of Children Study
URTI	Upper respiratory tract infection
WI	Wheezing illness
ZPBP2	Zona pellucida binding protein 2

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Laura Toivonen, Ville Forsström, Matti Waris and Ville Peltola. Acute Respiratory infections in early childhood and risk of asthma at age 7 years. *Journal of Allergy and Clinical Immunology*, 2019, 143: 407-410.

II Ville Forsström, Laura Toivonen, Kiara Homil, Matti Waris, Casper-Emil T Pedersen, Klaus Bønnelykke, Tuomas Jartti and Ville Peltola. Association of Asthma Risk Alleles With Acute Respiratory Tract Infections and Wheezing Illnesses in Young Children. *Journal of Infectious Diseases*, 2023, 228: 990-998.

III Ville Forsström, Matti Waris, Ville Peltola and Laura Toivonen. Rhinovirus Species in Acute Respiratory Tract Infections and the Risk of Asthma in Children. Manuscript.

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1 Introduction

Asthma is the most prevalent chronic disease in childhood and a major cause of morbidity worldwide (Asher & Pearce, 2014). While the pathogenesis of asthma is multifactorial and still incompletely understood, accumulating evidence has highlighted early life as a critical window in the development of childhood asthma. Wheezing illnesses during infancy and early childhood have been associated with an increased risk of subsequent asthma, particularly when those illnesses have been severe or accompanied with genetic susceptibility. Among the numerous viral pathogens, rhinovirus and respiratory syncytial virus have been most strongly associated with asthma risk. The exact nature of these associations, however, remains a subject of ongoing investigation. The most intriguing question is whether these associations are causal or only indicate the underlying predisposition to asthma.

Recent advances in genetics have shed light on genetic susceptibility to both asthma and respiratory infections. Several genetic loci have been identified that not only associate with increased asthma risk, but also with a heightened burden of early respiratory illnesses. For example, variants in the 17q locus and in the *CDHR3* gene have been found to associate with an increased risk of wheezing, severe asthma exacerbations and susceptibility to rhinovirus infections (Bønnelykke et al., 2014; Stein et al., 2018). These findings suggest that the interplay between genetic factors and environmental factors such as viral exposure may be crucial in shaping the course of immune system development toward asthma.

Understanding these complex interactions holds potential for both early identification of at-risk individuals and the development of targeted preventive strategies. By investigating the roles of specific viral pathogens and host genetic factors in asthma development, research can move closer to distinguishing children with transient wheezing illnesses from those who go on to develop persisting asthma. This dissertation aims to contribute to this rapidly advancing field of research by examining the associations between early life respiratory infections, genetic risk factors and the development of asthma in childhood, using comprehensive data from a prospective birth cohort and two complementary clinical studies.

2 Review of the Literature

2.1 Viral Respiratory Infections

2.1.1 Epidemiology

Respiratory tract infections are the most common type of infection across all age groups, and a major reason for primary care contacts (Finley et al., 2018). They are frequent in both adults and children and place a significant burden on the healthcare systems worldwide (Niederman & Torres, 2022).

While bacteria, and in rare cases fungi or parasites, are important causes of respiratory infections, the majority of respiratory infections are caused by viruses. This thesis focuses on viral respiratory infections. Most of the viral respiratory infections are self-limiting upper respiratory infections, but some viruses are more prone to cause even life-threatening lower respiratory infections (Nickbakhsh et al., 2016).

The most common respiratory infection is, as the name suggests, the common cold. It has a high incidence, with children under the age of two years experiencing on average 6 episodes per year, with median symptom duration of 9 days per episode (Toivonen et al., 2016). The incidence of common cold gradually declines as the age increases (Byington et al., 2015). Upper respiratory tract infections (URTI) are the leading cause of acute disease incidence globally and place a substantial burden on health care systems. In 2021, there were an estimated 12.8 billion URTI episodes in the world. The combined burden accounted for by URTIs and otitis media (OM) in the same year was estimated to be 6.86 million years lived with a disability (Sirota et al., 2025).

In the United States, common cold is estimated to cause 70 million missed workdays, 189 million missed school days and 126 million missed workdays by parents caring for a child with a common cold, per year. The economic loss due to common cold in the United States is estimated at 40 billion USD per year, while in Europe it has been estimated that the cost of single common cold episode to the society could be as high as 1102 euros (Montesinos-Guevara et al., 2022).

URTIs are typically caused by a rhinovirus, which can be detected in up to 50 percent of patients with common cold (Hemilä & Chalker, 2013; Mäkelä et

al., 1998). In young children, the incidence of rhinovirus infections is high, with an estimated 3-4 rhinovirus infections annually (Toivonen, Schuez-Havupalo, et al., 2016). In addition to the rhinovirus's role in common cold infections, rhinoviruses are associated with up to half of OM episodes and antibiotic treatments in children under the age of two, imposing a major burden of acute respiratory illness and antibiotic use on young children (Toivonen, Schuez-Havupalo, et al., 2016).

Respiratory syncytial virus or RSV is a major source of morbidity as well. The annual rate of RSV infections in children younger than two years of age is estimated at 0.3-0.4 episodes with median symptom duration of 10 to 11 days (Toivonen, Karppinen, Schuez-Havupalo, Teros-Jaakkola, et al., 2020). In 2019, RSV caused globally an estimated 33 million episodes of lower respiratory tract infection (LRTI) in children aged 0-60 months, especially during the first 6 months of life (Li et al., 2022). The RSV infections in children aged 0-60 months resulted in an estimated number of 3.6 million hospital admissions and 26,300 RSV-associated in-hospital deaths with global mortality estimated at 101,400 deaths per year (Li et al., 2022). In high-income settings, RSV-associated acute respiratory infections lead to the hospitalization of one in every 56 healthy term-born infants, causing substantial morbidity and health-care burden (Wildenbeest et al., 2023).

Viral respiratory tract infections have strong seasonal fluctuations with pathogen-specific patterns. In the northern hemisphere, the incidence of viral respiratory tract infections is typically lower during the summer months and peaks during autumn and winter for most pathogens (Weigl et al., 2007). Reasons for the seasonal fluctuation include cold weather which promotes virus survival and stability, and lower air humidity which enhances aerosol transmission and reduces mucous membrane defenses. The relative contribution of these factors, however, is not yet fully understood (Moriyama et al., 2020). A weekly fluctuation of influenza virus findings by the Department of Clinical Microbiology, Turku University Hospital is shown in Figure 1.

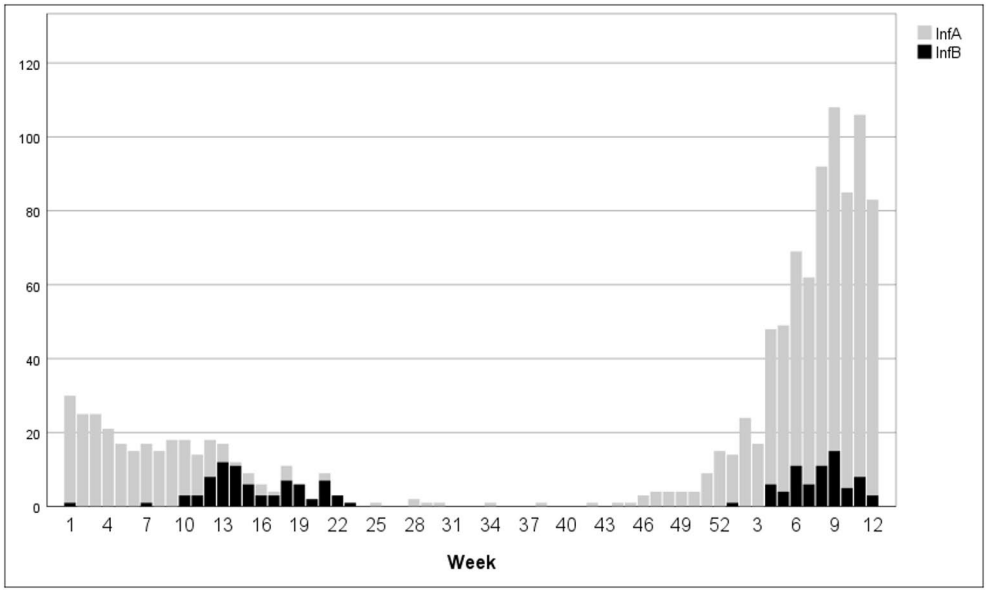

Figure 1. Weekly trend of detected Influenza in Turku University Hospital 01/2024 – 03/2025.

The COVID-19 pandemic raised public awareness of viral respiratory infections and led to temporary system-level and individual-level changes that affected transmission of other communicable respiratory infections as well. Containment and mitigation measures such as quarantines and closures of public spaces, remote work becoming more common, improved hand hygiene and social distancing decreased the number of influenza cases by up to 99% and led to the absence of one RSV epidemic (Harding et al., 2024; Parry et al., 2020). After the pandemic, relaxing anti-transmission practices and the so-called immunity debt has caused respiratory infection incidence to increase to higher levels than before pandemic (Ben Moussa et al., 2023; Xu et al., 2024). The long-term effects of the COVID-19 pandemic and its countermeasures on viral respiratory infection patterns and the overall health and well-being of children remain to be fully understood.

2.1.2 Etiology and Pathogenesis

The most common respiratory viruses causing a clinical illness are the rhinovirus, RSV, influenza viruses, parainfluenza viruses, metapneumovirus, coronaviruses, adenoviruses and bocaviruses which circulate in all continents either epidemically or as endemic viruses (Boncristiani et al., 2009). In children, rhinoviruses and RSV are the leading pathogens causing acute respiratory tract infections, early life wheezing illnesses and asthma exacerbations, and are therefore in the focus of this dissertation.

2.1.2.1 Rhinoviruses

Rhinoviruses frequently cause upper respiratory illnesses in children and adults and are the most common pathogens found in patients with common cold. Rhinoviruses are also associated with otitis media, sinusitis and lower respiratory illnesses and are a major factor in asthma exacerbations (Hemilä & Chalker, 2013; Johnston et al., 1995; Peltola et al., 2009). More than 10% of rhinovirus infections in young children are complicated by otitis media, and in 2.6% of rhinovirus infections, wheezing is observed (Toivonen, Schuez-Havupalo, et al., 2016). Rhinoviruses are also a major contributor to the hospitalization of children (Miller et al., 2007; Peltola et al., 2008). Among asymptomatic children below the age of two years, rhinovirus prevalence detected by polymerase chain reaction (PCR) may reach 9% (Toivonen, Schuez-Havupalo, et al., 2016).

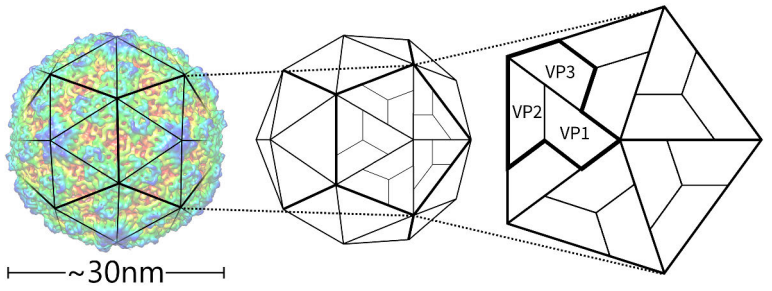

Figure 2. Rhinovirus structure. From left to right: cryo-electron microscopy reconstruction of RV-A2, symmetry of the virus particle and symmetry of the three surface-exposed capsid proteins. Figure courtesy of Petri Susi.

Rhinoviruses are single-stranded ribonucleic acid (RNA) viruses, belonging in the *Enterovirus* genus in the family of Picornaviruses. Based on their genetic relationships, rhinoviruses are classified into species A, B and C (McIntyre et al., 2013; Simmonds et al., 2020). Species A and C are more prevalent and more frequently associated with severe disease than species B, which is more frequently detected in asymptomatic subjects (Jackson & Gern, 2022; Lee et al., 2012). To date, at least 169 rhinovirus types are recognized among the species (Basnet et al., 2019). Rhinoviruses have an icosahedral capsid structure which consists of multiple copies of four capsid proteins. The capsid proteins VP1, VP2 and VP3 lay on the surface of the capsid, while the VP4 is located on the internal surface of the capsid. The structure of rhinovirus is presented in Figure 2. Inside the capsid is the tightly packed viral RNA genome. The genome has a single long open reading frame, encoding a large precursor polyprotein. This polyprotein is divided into three regions and further into 11 individual functional viral proteins as shown in Figure 3.

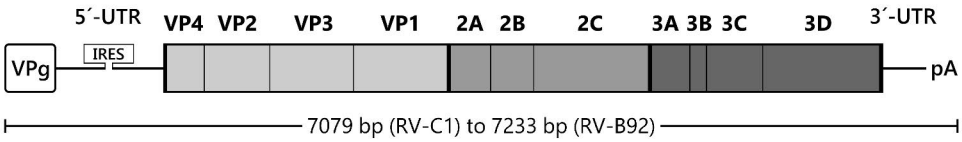

Figure 3. Rhinovirus genome. Different shades represent the three genomic regions. VP1-VP4 encode the capsid proteins, while 2A-3D encode functional proteins involved in protein processing and genome replication. Figure courtesy of Petri Susi.

Rhinovirus transmission can occur by self-inoculation after hand-to-hand contact or contact with virus-contaminated objects or surfaces, by airborne manner as aerosols, or by larger droplets following close contact with an infected person (Esneau et al., 2022). After transmission, rhinoviruses use three different cellular membrane receptors to enter the host cell. These are the intercellular adhesion molecule 1 (ICAM-1) which is used by the majority of RV-A subtypes and all RV-B subtypes, low density lipoprotein receptor (LDLR) family members which are used by 12 RV-A subtypes, and cadherin-related family member 3 (CDHR3) which is used by RV-C (Basnet et al., 2019).

Intercellular adhesion molecule 1 (ICAM-1) is a transmembrane glycoprotein typically expressed at very low levels by epithelial and endothelial cells and leukocytes. ICAM-1 has the capacity to be rapidly upregulated by cytokine stimulation, which helps to regulate leukocyte migration from blood to sites of inflammation (Hubbard & Rothlein, 2000). ICAM-1 regulates the leukocyte migration by binding to two integrin receptors, leukocyte function-associated antigen and macrophage-1 antigen (Bella et al., 1998; Diamond et al., 1990). In 1989, ICAM-1 was recognized as a cellular receptor for the so-called major group rhinoviruses, constituting all RV-B and most of RV-A types (Greve et al., 1989). To initiate a rhinovirus infection, the N-terminal immunoglobulin domain of ICAM-1 binds to the viral protein 1 (VP1) and viral protein 2 (VP2) capsid proteins of the rhinovirus. This triggers endocytosis, which allows the viral RNA to enter the cytosol (Basnet et al., 2019). In addition to rhinovirus, ICAM-1 is used by other pathogens such as coxsackievirus A21 and *Plasmodium falciparum* (Bella et al., 1998).

In the low-density lipoprotein receptor family, there are at least three glycoproteins known to bind rhinoviruses: low density lipoprotein receptor, very low-density lipoprotein receptor, and LDLR-related protein (Basnet et al., 2019). These glycoproteins are expressed in almost all tissues, and their role in the normal function of the cell is to transport cholesterol-containing lipoprotein particles from the circulation into the cell. Loss-of-function mutations in the encoding *LDLR* gene cause familial hypercholesterolemia (Beglova & Blacklow, 2005; Matsui et al.,

2010). Rhinovirus endocytosis is initiated when capsid protein VP1 interacts with the domains D2 and D3 of the LDLR (Basnet et al., 2019).

CDHR3 is a transmembrane glycoprotein expressed highly in airway and gastrointestinal epithelia, brain and fallopian tubes (Basnet et al., 2019; GTEx Portal, 2025). The normal function of CDHR3 is yet unknown. CDHR3 is the only known receptor to be used by rhinovirus species C (Bochkov et al., 2015). A single nucleotide polymorphism (SNP) rs6967330-A in *CDHR3* gene is associated with higher CDHR3 expression, increased RV-C binding and increased viral replication (Bochkov et al., 2015). The rs6967330-A allele is also associated with childhood asthma with severe exacerbations (Bønnelykke et al., 2014).

The large number of rhinovirus types, little cross-immunization between them and many rhinovirus types circulating in the population simultaneously contribute to the high prevalence of rhinovirus infections (Jackson & Gern, 2022). Rhinoviruses circulate around the year in the community, but infection rates are highest in spring and fall. The severity of rhinovirus disease increases in the winter months (Lee et al., 2012; Moriyama et al., 2020). The increased severity is thought to be at least partially related to the optimal replication temperature of 33°C of the rhinovirus, due to the less efficient antiviral response at lower than body temperatures (Foxman et al., 2015).

2.1.2.2 Respiratory Syncytial Virus

Respiratory syncytial virus is the leading cause of respiratory illnesses and hospitalizations in infants, with an estimated 55,000 to 200,000 annual deaths in children under the age 5 years globally (Shi et al., 2017). Almost all children are infected with RSV by two years of age. The peak incidence in RSV infections is between 3 and 10 months of age (Thomas et al., 2021). Peak incidence in hospitalization, however, is before the age of three months (Toivonen, Karppinen, Schuez-Havupalo, Teros-Jaakkola, et al., 2020; Uusitupa et al., 2024). The disease is most serious in infants under the age of 1 year (Bergeron & Tripp, 2021; Shi et al., 2017).

RSV is a single-stranded negative-sense RNA virus, belonging to genus *Pneumoviridae* and is classified into two distinct subgroups A and B based on the genetic sequence of protein G which the virus uses for attachment (Bergeron & Tripp, 2021). A schematic of the RSV genome is presented in Figure 4. The role of nonstructural genes (NS) is not fully understood. Nucleoprotein (N), phosphoprotein (P) and RNA polymerase (L) are important in the replication, while matrix (M), surface fusion (F), small hydrophobic (SH), and glycosylated attachment glycoproteins (G) are important structural and surface proteins, surface fusion protein being critical for cell entry.

Figure 4. RSV genome with gene segments roughly to scale. Figure reproduced with the permission of Springer Nature, from Viral Infections of Humans, Paramyxoviruses: Respiratory Syncytial Virus and Human Metapneumovirus; Crowe, James E. Jr; Williams, John V. 2014.

RSV transmission occurs when respiratory secretions from infected individual inoculate the nasopharyngeal or conjunctival mucosa, either directly as droplets or aerosol transmission or via several types of surfaces. The virus may remain viable on hard surfaces for up to 6 hours and on skin for up to 20 minutes (Piedimonte & Perez, 2014). After transmission, protein G interacts with cell surface factors such as CX3C motif chemokine receptor 1, heparan sulphates and chondroitin sulphate B glycosaminoglycans, facilitating the initial attachment. This allows protein F to contact its receptor, nucleolin, which leads to ribonucleoprotein complex being released into the host cell cytoplasm beginning the replication process (Kaler et al., 2023).

RSV primarily infects ciliated human airway epithelial cells in the upper respiratory system (Bergeron & Tripp, 2021). After that, the virus may spread to the lower respiratory system and bronchioles, where viral replication is more effective (Carvajal et al., 2019). Spreading to the lower respiratory system happens frequently in previously uninfected individuals, typically infants, causing the classical lower respiratory tract infection of bronchiolitis or viral pneumonia (Kaler et al., 2023). This leads to the deterioration and sloughing of epithelial cells, syncytium formation, mucus hypersecretion and increased permeability of the capillaries, drawing pro-inflammatory cells to the site of infection (Carvajal et al., 2019). Interstitial swelling follows and surfactant function is disrupted, which may lead to respiratory distress (Dargaville et al., 1996).

The seasonality of RSV infections varies globally. In the northern hemisphere, RSV rates increase during late autumn and peak in the winter months, with low activity after spring. In the southern hemisphere the seasonality is countercyclical. In most countries, the onset and peak of RSV activity differ by only 1-3 weeks from year to year (Obando-Pacheco et al., 2018). In Finland, RSV activity may differ more from year to year with major and minor epidemics and the RSV subgroup alternating. The peak incidence alternates between spring and turn of the year (Gunell et al., 2016; Waris, 1991). The COVID-19 pandemic and the nonpharmaceutical interventions implemented to slow its spread have changed the pattern in Finland, however. There was no RSV epidemic in winter and spring 2020-2021 during the strict interventions, and the epidemics in the following two winters started earlier than usual and were larger in scale (Harding et al., 2024).

2.1.3 Risk Factors

The risk factors for viral respiratory illnesses range from genetic disorders of the immune system to age, daycare attendance and the number of social contacts. Prematurity is associated with an increase in severity of rhinovirus infections in infants (Costa et al., 2014). This may be due to the altered and incomplete lung development, other chronic conditions associated with prematurity and lack of maternal immunoglobulin G (IgG) antibodies. The IgG is the only antibody capable of passing through the placenta, the transfer being mediated by the neonatal Fc receptor. Antibody transfer begins at 13th gestational week, increasing throughout the gestation. Majority of the IgG is transferred in the last four weeks of pregnancy (Palmeira et al., 2011). Neonates rely on this maternal antibody transfer for protection against infections until their ability for own antibody generation increases. Disrupted antibody transfer during pregnancy due to prematurity, or for example maternal human immunodeficiency virus (HIV) infection, increases the risk for a variety of infections (Semmes et al., 2021).

Maternal IgG antibodies start to fade after birth and disappear before the age of 12 months. During this time, breastfeeding supports the immunity system with immunoglobulin A (IgA) antibodies as well as protective factors such as lactoferrin and oligosaccharides which prevent mucosal microbe attachment. The IgA antibodies are thought to explain the well-documented protective effect of breastfeeding against infections generally, and against gastrointestinal and respiratory tract infections specifically (Duijts et al., 2009). The data on possible protective effect of breastfeeding against URTIs are inconclusive, however (Duijts et al., 2009; Tromp et al., 2017).

Immunodeficiencies increase the risk for various infections and cause susceptibility to more severe forms of infection. Of the primary immunodeficiency disorders, antibody deficiencies and T-cell disorders are especially important regarding viral infections. Primary antibody deficiencies are the most common primary immunodeficiencies. In primary antibody deficiencies (PAD), antigen-specific antibody production is defective, which results in conditions ranging from asymptomatic to life-threatening. Examples of primary antibody deficiencies are transient hypogammaglobulinemia of infancy, X-linked agammaglobulinemia and common variable immunodeficiency. Regardless of the cause, PAD increases the risk for a multitude of viral, bacterial and parasitic infections. Although usually less of a consequence than bacterial infections, the risk for recurrent viral URTIs and ear-nose-throat infections is also increased (Driessen & Van Der Burg, 2011). T-cell disorders impair cell-mediated immunity and manifest as an unusually frequent and severe viral, bacterial and fungal infections. An example of a severe form of T-cell deficiency is severe combined immunodeficiency, which leads to life-threatening

infections early in life (Aranda et al., 2024). Immunodeficiencies, however, are very rarely the cause of recurrent respiratory infections in children.

Genetic factors other than recognized immunodeficiencies can also predispose to more frequent or severe viral respiratory infections. These genetic interactions are poorly understood, however. Identical twins have an increased concordance of severe RSV infection, which suggests shared genetic predisposition (Thomsen et al., 2008). Single nucleotide polymorphisms in *IL28B* correlate with susceptibility and severity of RSV infections in infants (Astudillo et al., 2019; Giamberardino et al., 2022). SNPs in *DDX58*, *JAK2* and *VDR* genes have been reported to associate with a higher burden of common cold symptoms (Loisel et al., 2016). Polymorphisms in Toll-like receptor 2 (*TLR2*) and Toll-like receptor 4 (*TLR4*) genes have been found to associate with recurrent and severe respiratory infections and episodes of otitis media (Teräsjärvi et al., 2024). On the other hand, minor variants in the *IFI44L* gene are associated with lower rates of respiratory infections, antibiotic treatments and lower rate of otitis media episodes (Lempainen et al., 2021). In the wake of the recent pandemic, several genetic risk factors that increase susceptibility to and severity of COVID-19 infections have been identified (Ishak et al., 2022).

Of the environmental factors, maternal smoking during pregnancy and exposure to indoor tobacco smoke increase susceptibility to respiratory infections (Fleming et al., 1987; McEvoy & Spindel, 2016). High levels of indoor pollution also increase the risk for respiratory infections (Pandey et al., 1989). Crowded living is reported to increase risk for respiratory infections, especially in children younger than 36 months (Fleming et al., 1987), but evidence is conflicting (Larson et al., 2010). Increased contacts through daycare and having older siblings are risk factors for viral respiratory infections (Fleming et al., 1987; Langer et al., 2022). The increase in viral respiratory infections after the start of daycare seems to be transient, however (Schuez-Havupalo et al., 2017).

Recently, airway microbiome and certain microbiotas have been proposed as risk factors for respiratory infections and asthma exacerbations (Hasegawa & Camargo, 2015; Toivonen, Hasegawa, et al., 2019). For example, certain neonatal respiratory microbiome types are associated with more severe RSV infections and *Haemophilus*, *Streptococcus* and *Moraxella* abundance during an RSV infection is associated with more severe infection while *Dolosigranulum* and *Corynebacterium* are associated with milder disease (Kristensen et al., 2024). Higher abundance of *Haemophilus* and *Moraxella* might also modulate airway inflammation during RSV bronchiolitis and potentially contribute to subsequent wheezing in childhood (Zhang et al., 2020). *Moraxella* sparsity on the other hand, is reported to associate with higher asthma risk (Toivonen, Karppinen, Schuez-Havupalo, Waris, et al., 2020). Rhinovirus infections can induce changes in the upper airway microbiome, for example by promoting abundance of *Moraxella* (Kloepfer et al., 2017). Even asymptomatic viral infections

in early life have been associated with specific microbiota dynamics, which in turn associate with an increased frequency of viral respiratory tract infections during the first year of life (de Steenhuijsen Piters et al., 2022). The functional understanding of the microbiota and their interactions with host immunity is still lacking but could in future guide the development of microbiome-based treatments (Di Simone et al., 2023). Associations between certain nasopharyngeal metatranscriptome profiles and risk of asthma have also been reported (Raita et al., 2022).

2.1.4 Clinical Presentation

Respiratory infections can range from asymptomatic to life-threatening infections. Most viral respiratory infections are self-limiting and mild, but some may may be severe in a susceptible population (e.g. RSV-induced bronchiolitis in infants). Viral respiratory infections typically have an acute onset and last for days or, at most, a couple of weeks in immunocompetent hosts. Although most respiratory infections are viral, it is often hard or impossible to distinguish between viral and bacterial infections based on the symptoms alone.

In upper respiratory tract infections, infection involves mostly upper respiratory tract (above the larynx) and includes infections of the ear, nose and sinuses and throat. Examples of these infections are otitis media (OM), laryngitis, sinusitis and common cold. In lower respiratory tract infections, infection involves lower respiratory tract such as bronchi and lung parenchyma. Lower respiratory tract infections include infections such as bronchitis, bronchiolitis and pneumonia. In respiratory tract infections, symptoms can be diverse and strict classification by anatomical regions is often not useful nor clinically relevant. For example, sore throat, nasal congestion, runny nose, headache, cough, fever and muscle pain are all typical symptoms associated with common cold (Heikkinen & Järvinen, 2003; Witek et al., 2015). The mix of pathological and clinical nomenclature both in clinical practice and in the literature is a major challenge in the research of respiratory infections. The naming conventions for some of the clinical syndromes presented in the following paragraphs may therefore vary significantly by country and region.

URTIs caused by rhinoviruses and a wide range of other viruses are referred to as common cold. In some cases, influenza is regarded as its own entity, although it cannot reliably be differentiated from other respiratory infections based on symptoms alone (Heikkinen & Järvinen, 2003). The symptoms of an URTI arise after an incubation period, which has considerable variation among the different viruses, ranging from a minimum of 10–12 hours for the rhinovirus to a maximum of 1–7 days for the influenza virus (Heikkinen & Järvinen, 2003). The most common symptoms of common cold in children are nasal congestion, runny nose, cough and sneezing, followed by fever and headache. These signs last longer in children than

in adult population, typically for 10 days or more (Pappas et al., 2008). Many distinct diagnoses overlap with common cold or are associated with common cold viruses, such as pharyngitis, laryngitis, sinusitis and OM.

Pharyngitis is caused by an inflammation of the pharynx and surrounding tissues. The etiology of pharyngitis is typically viral or bacterial, with rhinovirus, adenovirus, coxsackievirus, coronavirus, RSV and Epstein-Barr virus being the most common viral agents. Main symptoms are sore throat, odynophagia and fever, which typically peak within 3–5 days of symptom onset and resolve by day 10 (Sykes et al., 2020).

Laryngitis or croup is an infection of the larynx, a viral infection typically caused by parainfluenza virus. It is often preceded by symptoms of common cold and is characterized by the abrupt onset of a barking cough, inspiratory difficulty and stridor and hoarseness, most commonly at night. Symptoms of laryngitis usually resolve within 48 hours (Johnson, 2014). Laryngitis is sometimes considered a lower respiratory tract infection.

Sinusitis is an inflammation of the nasal sinuses. The most common cause of acute sinusitis is a viral infection associated with common cold. Symptoms of viral sinusitis typically start to alleviate after few days and typically last for 7–10 days, sometimes considerably longer. Bacterial sinusitis can sometimes occur as a complication of common cold and may require antibiotic treatment (Abzug, 2014; Nocon & Baroody, 2014).

Another typical bacterial complication of viral URTI is otitis media. Otitis media is very common: by 3 years of age, 83% of children have at least one episode, with almost half experiencing recurrent episodes of otitis media (Teele et al., 1989). Although otitis media can be caused by viruses alone, the most typical pathogens isolated are *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis* (Sillanpää et al., 2016). The necessity of antibiotic treatment in otitis media has been debated, in part because of the varying criteria used. When only children who meet stringent diagnostic criteria are included, the benefit of antimicrobial treatment seems apparent as almost half of the children treated with placebo have treatment failure (Tähtinen et al., 2011).

Lower respiratory tract infection (LRTI) is a term used interchangeably to include bronchitis, bronchiolitis and pneumonia. Pneumonia is usually differentiated from bronchitis and bronchiolitis by the evidence of parenchymal involvement, either by physical examination or the presence of infiltrates on chest X-ray. Pneumonia is typically caused by viruses or bacteria. In infants and children younger than 5 years of age, viruses are reported as the most common etiology of pneumonia, the single most common viral pathogen being RSV, while bacteria dominate in children older than 5 years (Jain et al., 2015). There are significant challenges in establishing the causal agent of pneumonia, however. As the microbiological

samples are usually obtained from the upper airways, the results may not reflect the pathogens in lower airways. This can lead to overreporting of viruses as the aetiologic agent. In addition, distinguishing colonisation from infection can be difficult (Ruuskanen et al., 2011). The onset of viral pneumonia is gradual and usually associated with preceding upper respiratory tract symptoms. The most common symptoms associated with viral pneumonia are cough, fever, fast breathing, runny nose, loss of appetite and eventually, wheezing. Rhinitis and wheezing may be more common in viral than bacterial pneumonias, and biomarkers of infection are usually only mildly elevated (Ruuskanen et al., 2011). The length of pneumonia symptoms varies considerably depending on the severity of the illness and the aetiologic agent (Tumer et al., 2006).

Bronchiolitis is an inflammation of the smallest airways, bronchioles. Worldwide the definition is inconsistent but in Europe, bronchiolitis is defined as the first obstructive respiratory illness in children younger than 1 years of age (Alahengitystieinfektiot (lapset). Käypä hoito -suositus., 2024; Dalziel et al., 2022). Bronchiolitis is a common viral disease, and one of the most substantial health burdens in infants and young children worldwide (Vos et al., 2016). Approximately one in three infants develop bronchiolitis during the first year of life, with the incidence of bronchiolitis peaking at 3 to 6 months of age (NICE guideline, 2015). Most bronchiolitis episodes are treated in an outpatient setting, but hospitalization is also common (Wolf et al., 2021). In the developed countries, bronchiolitis is the most common reason for an admission to hospital before the age of 1, with approximately 2-3% of infants admitted yearly (Dalziel et al., 2022). Most cases of bronchiolitis are caused by RSV, but rhinovirus, human metapneumovirus, parainfluenza viruses and adenoviruses are also possible aetiologic agents (Dalziel et al., 2022; Smyth & Openshaw, 2006).

The diagnosis of bronchiolitis is clinical (Florin et al., 2017). Usually, symptoms of URTI precede bronchiolitis for up to 2 days, after which the infection progresses to lower respiratory tract. Typical symptoms of bronchiolitis include cough and signs of respiratory distress such as tachypnoea and increased work of breathing observable by intercostal retractions and the use of abdominal muscles. Auscultatory findings include crackles and wheezing. Young infants may also present with apnoea. Rapid variation in the clinical findings is characteristic for bronchiolitis (Dalziel et al., 2022). Symptoms usually worsen for the first few days. After 3-5 days of illness, the peak severity of symptoms is reached and improvement begins, with 90% of infants recovered from symptoms within 3 weeks (Dalziel et al., 2022). There is no beneficial interventional therapy for bronchiolitis, and treatment is supportive (Dalziel et al., 2022).

Bronchitis is an inflammation of the bronchi, which causes cough and frequently associates with URTI. Obstructive bronchitis is defined as a virus-induced wheezing

illness in children older than 1 year (Alahengitystieinfektiot (lapset). Käypä hoito -suositus., 2024). Wheezing during viral infections is common in young children but typically ends by 3 years of age. In older children, wheezing illnesses have a significant overlap with asthma and differentiating asthma and recurring wheezing illnesses is difficult (Ducharme et al., 2014; Global Initiative for Asthma, 2024). Based on parental questionnaires, almost half of children have at least one wheezing illness by the age of 6 years (Martinez et al., 1995). Rhinovirus and RSV are the most common causative agents in wheezing illnesses (Lehtinen et al., 2006). Otitis media is a typical coinfection in wheezing illness, observed in as many as 44% of children with wheezing illness. Although infiltrates in chest x-ray may be seen in wheezing illnesses, alveolar pneumonia as a coinfection is observed only in 10% of the children (Lehtinen et al., 2006).

2.1.5 Viral Diagnostics

The aetiological diagnosis of viral respiratory infections relies on laboratory diagnostics. Nucleic acid amplification by PCR, direct fluorescent antibody and rapid antigen detection tests, virus cultivation, and in some cases blood serology tests may be used (Loeffelholz et al., 2016). Depending on the chosen test and type of infection, the sample may be taken with a nasopharyngeal (NP) aspiration, nasal wash, NP flocked swab, bronchoalveolar lavation or by drawing a blood sample. In the last decades, NP flocked swabs and either PCR or antigen tests have become the mainstay of respiratory virus diagnostics, improving sensitivity and specificity and reducing the test turnaround time (Ginocchio & McAdam, 2011).

NP flocked swab is easier to collect than NP aspiration or nasal wash from older children. NP flocked swabs are noninferior to NP aspiration and nasal wash in the detection of respiratory viruses (Abu-Diab et al., 2008). The type of test determines how the sample should be handled and transported. Each hour of delay before inoculation makes successful viral culture more unlikely, whereas antigen and PCR tests do not need the viruses to be viable and especially PCR analysis can be done successfully after extended periods of transportation and storage (Jerome et al., 2002).

PCR test has become the golden standard for respiratory virus diagnostics for its high sensitivity and specificity (Ginocchio & McAdam, 2011). Multiplex PCR tests can be used to simultaneously detect up to 16 common respiratory virus pathogens, with results available even in less than 1 hour (Huang et al., 2017). Multiplex PCR can also include bacterial pathogens such as *Bordetella pertussis* and *Mycoplasma pneumoniae*. Rapid antigen detection tests can be used effectively in an ambulatory setting. Automated multianalyte antigen tests are easy to use and have a high specificity and moderate to high sensitivity in detecting respiratory viruses, with

positive results reported in as little as 20 minutes (Gunell et al., 2016). Direct fluorescent antibody test can be performed in 30 to 60 minutes, although the process is more labour intensive than rapid antigen detection test (Landry, 2009). Rapid antigen detection test and direct fluorescent antibody test are not suitable for the detection of rhinoviruses due to the high diversity of rhinovirus types and a lack of common antigen. Cell cultures have become obsolete in clinical practice due to the long detection times of 3 to 7 days as well as inferior sensitivity and specificity (Ginocchio & McAdam, 2011).

Although rhinoviruses have been cultivated for a long time, rhinovirus C was identified as late as 2007, because it does not grow in standard cell culture (Lee et al., 2007). Blood serology is rarely used in respiratory virus diagnostics except for suspected infectious mononucleosis (Leung et al., 2024). In the future, next-generation sequencing may be particularly helpful in the detection of previously unknown respiratory viruses (Wang et al., 2022).

2.1.6 Treatment and Prevention

The treatment of viral respiratory infections depends on the causal pathogen and the severity of the infection. Some infections require no treatment at all while some require supportive care. In some cases, however, targeted treatment options are available, such as antiviral drugs in influenza (Gao et al., 2024). There is no antiviral treatment approved for rhinovirus, and treatment of rhinovirus infections such as common cold is supportive, when needed. In trials of regular vitamin C supplementation, it has been shown that vitamin C could reduce the duration of common cold, but this has not been replicated in therapeutic trials (Hemilä & Chalker, 2013). Zinc has also been used for treatment of common cold and may reduce the duration of ongoing colds, although little or no difference in symptom severity was observed (Nault et al., 2024). There is no evidence of steam inhalation, *Echinacea* or non-steroidal anti-inflammatory drugs reducing the symptoms or the duration of common cold, while antihistamines may slightly reduce runny nose and sneezing (Arroll, 2011). Nasal decongestants are frequently used in common cold and may reduce subjective nasal congestion in adults, but their effectiveness and safety in children remains to be determined (Deckx et al., 2016).

Treatment of RSV infections is similarly supportive. RSV-induced bronchiolitis treatment is limited to respiratory support and other supportive care. Steroids, inhaled hypertonic solution, and bronchodilators are not recommended due to the lack of evidence (Virgili et al., 2024). High-flow nasal cannula therapy may have benefits over low-flow oxygen in some infants (Armarego et al., 2024).

Vaccines and antibody administrations are effective in reducing the number and severity of viral respiratory infections. Vaccines are available against influenza

viruses and are significantly more effective in children than in the elderly (Tanner et al., 2021). Because of the antigenic heterogeneity amongst the rhinovirus species, rhinovirus vaccine has long been considered unrealizable, however (Glanville & Johnston, 2015; Vandini et al., 2019). Vaccines for RSV are already available, and further vaccine development is ongoing (Topalidou et al., 2023). Current vaccines against RSV, however, are only indicated in the adult population.

Major steps have recently been taken in the prevention of RSV infections in infants. The Abrysvo® vaccine was approved in Europe in 2023 for the passive immunization of infants by maternal administration during pregnancy. A single dose of bivalent RSV vaccine given to the mother during the third trimester reduces the burden of severe RSV respiratory infections in infants by up to 80 percent (Kampmann et al., 2023). Additionally, a long-acting monoclonal antibody nirsevimab was approved in 2022 for the prevention of RSV-associated lower respiratory tract infections in the European Union. Nirsevimab prophylaxis has effectiveness of more than 80 percent in preventing severe RSV lower tract infections and hospitalizations due to RSV infections (Ares-Gómez et al., 2024; Hammitt et al., 2022). The effectiveness is similar in preterm infants (Griffin et al., 2020). Real-world surveillance studies of Nirsevimab have confirmed the findings of randomized trials, with prophylaxis effectiveness of 70–90% (Kuitunen & Renko, 2024). Extensive nirsevimab prophylaxis began in Finland on the RSV season of 2024–2025 and continues on RSV season 2025–2026. Nirsevimab prophylaxis is provided for children in risk groups under the age of 1 year and, with reservations, to children under the age of 3 months (Nirsevimabi Respiratory Syncytial -Viruksen (RSV) Aiheuttaman Alempien Hengitysteiden Infektion Estossa, 2025).

Probiotics may be useful in preventing URTIs such as common cold according to a 2015 review, although the quality of the evidence is very low (Hao et al., 2015). Vitamin C does not seem to reduce the incidence of common cold in the general population, although it may be useful for people exposed to short periods of severe physical exertion (Hemilä & Chalker, 2013). Good hand hygiene such as regular hand washing and using antiseptic hand rub as well as hand hygiene programmes reduce the number of viral respiratory infections in children and adults. Surgical masks probably make little or no difference in community setting but may be useful in health-care settings (Jefferson et al., 2023). Physical distancing is useful in reducing the transmission of all respiratory viral infections (Chu et al., 2020).

2.2 Childhood Asthma

2.2.1 Epidemiology

Asthma is the most prevalent chronic disease in children globally and among the top 20 causes of disability-adjusted life years (DALY) for children of all ages (Asher & Pearce, 2014; Serebrisky & Wiznia, 2019). Asthma is also the most prevalent chronic respiratory disease globally in adult population, with an estimated 300 million people with asthma (Bahadori et al., 2009). Annually, 400,000–500,000 deaths and 22.8 million DALYs are attributed to asthma (Soriano et al., 2017).

The prevalence of asthma varies substantially between countries, with over 10-fold differences observed in the International Study of Asthma and Allergies in Childhood (ISAAC) (Beasley et al., 1998). In affluent countries, asthma symptoms appear to be more prevalent, although less severe (Lai et al., 2009). This may indicate that in lower-income countries, a large portion of less symptomatic asthma is undiagnosed. The prevalence ranges widely even in Europe from 1.4% in Bosnia-Herzegovina to 20.6% in Sweden (Dierick et al., 2020). The rise in prevalence of asthma symptoms in children has plateaued in recent years, with an estimated one in 20 children having asthma (Asher et al., 2021; Lai et al., 2009). In 2019 in Finland, 2,818 new children of 0–14 years of age received reimbursement for asthma medication, with numbers decreasing from previous years, especially in boys of age 0–4 years (Astma. Käypä hoito -suositus., 2022).

Due to its high prevalence, asthma places a substantial burden on healthcare and economic systems. The economic costs of asthma can be direct, or indirect due to absence from work and school, with direct costs exceeding indirect costs (Bahadori et al., 2009; Dierick et al., 2020). A 2018 study from the United States estimated the total cost of asthma in USA to be 81.9 billion dollars annually, with 3-billion-dollar costs from missed school days only (Nurmagambetov et al., 2018). In Western Europe, 43% of the children diagnosed with asthma had lost schooldays because of asthma in the last 12 months, while 17% of the parents lost workdays for child's asthma (Rabe et al., 2004). The burden of asthma on quality of life is significant, with chronic asthma symptoms being strongly associated with reduced quality of life scores (Lang et al., 2010).

2.2.2 Pathophysiology and Pathogenesis

Asthma is a heterogenous disease with different observable phenotypes and diverse, only partially understood immunopathophysiology. The common denominator in all asthma types is the chronic inflammation of the airways, with respiratory symptoms and obstructive expiratory airflow limitation, resulting from a reduction in the

diameter of the airways. This chronic inflammation is characterized by the infiltration and activation of immune cells in the airways. The interactions between the immune cells such as dendritic cells, eosinophils, neutrophils, lymphocytes, mast cells and structural cells lead to hyperresponsiveness of the bronchi. In mild cases, the hyperresponsiveness is reversible with bronchodilators. In severe forms of the disease, mucus formation may cause fixed airway obstruction while airway remodelling contributes to the persistence of symptoms (Hammad & Lambrecht, 2021).

In the past, classification of asthma has been solely based on the asthma phenotypes. The Global Initiative for Asthma has previously recognized allergic or atopic asthma, non-allergic asthma, late-onset asthma, asthma with persistent airflow limitation, cough predominant asthma and asthma with obesity, but this classification does not describe the underlying disease process (Hammad & Lambrecht, 2021).

In preschool children, the phenotypes of episodic viral wheeze and multi-trigger wheeze have been recognized. The episodic viral wheeze phenotype is more frequent in infancy and is characterized by wheezing symptoms only during viral infections. The multi-trigger wheeze phenotype, on the other hand, is more likely to persist into school age and wheezing symptoms may occur also in response to different factors such as allergens and exercise (Foppiano & Schaub, 2023).

In school-age children, two phenotypes are classically identified: allergic and nonallergic asthma. Allergic asthma is characterized by immunoglobulin E (IgE) specific allergen sensitization and the presence of atopic diseases and is strongly associated with eosinophilic inflammation. Nonallergic asthma is another form of asthma in children, with no allergic sensitization or atopic diseases (Foppiano & Schaub, 2023; Raedler et al., 2015).

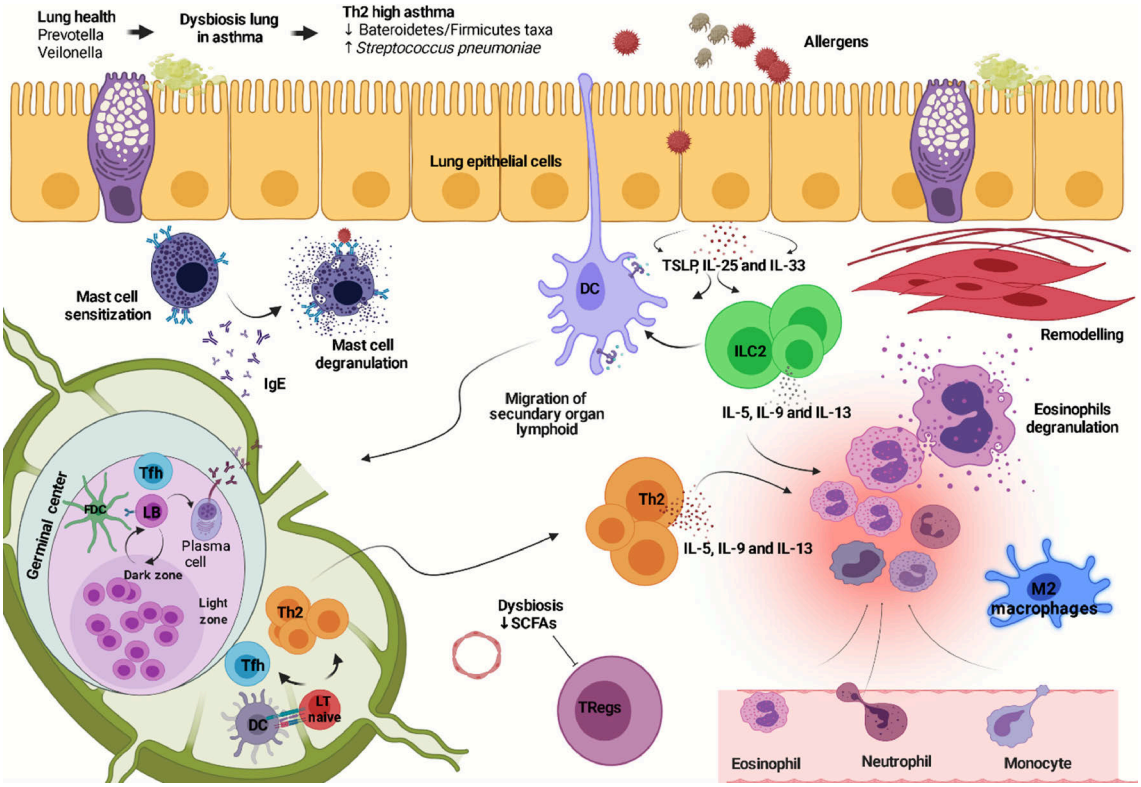

Figure 5. Pathophysiological mechanisms in type 2-high asthma. Figure reproduced with the permission of Elsevier from (Menegati et al., 2023)

Endotypes, in contrast with phenotypes, are subtypes of asthma defined by pathophysiological mechanisms. The endotypes can help explain the differing responses on treatments from child to child and guide the research, diagnostics and individual treatment in the future (Conrad et al., 2020). Examples of the endotypes are type 2-high and type 2-low asthma. In type 2-high asthma, type 2 inflammation is observed, mediated by T helper 2 lymphocytes and type 2 innate lymphoid cells via the cytokines interleukin 4, 5 and 13 which in turn promote eosinophilic airway inflammation (Scotney et al., 2023). The pathophysiological mechanism of type 2-high asthma is presented in Figure 5. Type 2-low endotype is more complex and has no identified biomarkers (Hammad & Lambrecht, 2021). Type 2-high asthma has been assumed as the most common endotype of asthma, but this is disputed. A recent study using transcriptomic profiling suggests that the ratio of endotypes can differ between ethnicities and type 2-low asthma can be more common than presumed (Yue et al., 2025).

The effect of viral infections on the pathogenesis of asthma is subject to discussion. Acute wheezing illnesses with rhinovirus and RSV predict recurrent

wheezing and later asthma (Kotaniemi-Syrjänen et al., 2003; Lukkarinen et al., 2017; Ruotsalainen et al., 2013). Especially rhinovirus species A and C are associated with wheezing illnesses in early childhood and severe asthma exacerbations later in childhood, while RV-B infections do not increase the risk for exacerbations to a similar extent (Kloepfer et al., 2014; Zheng et al., 2017). The causality of the association between early life viral infections and asthma is debated.

Considering the complex interactions between immune cells, cytokines and other tissues in the development of asthma, it is justifiable to assume that viruses and other pathogens can influence the process. Viral respiratory tract infections can activate type-2 inflammatory responses in the lungs (Fahy, 2015; Jartti et al., 2020). RSV-induced bronchiolitis typically happens while the lungs are still developing and sustained epigenetic or cell behaviour changes are possible during this time (Bégin & Nadeau, 2014; Jartti & Gern, 2017). RSV infection leads to an increased expression of nerve growth factor (NGF) in the developing lungs (Hu et al., 2002). In addition to controlling sensorineural development, NGF is a major determinant of neurogenic inflammation, and its overexpression could lead to airway hyperreactivity (Jartti & Gern, 2017). Treatments to prevent viral infections and modify host responses have been studied with the aim of asthma prevention. Oral prednisolone treatment in rhinovirus induced wheezing illnesses has been trialled in the prevention of asthma. The results have been inconclusive, however, although some promise was seen in children with high rhinovirus loads (Jartti et al., 2015; Koistinen et al., 2017). Corticosteroid therapy during RSV bronchiolitis has not been effective in the prevention of asthma (Massie et al., 2000). Palivizumab prophylaxis to prevent severe RSV disease in preterm infants decreased recurrent wheezing during the first 6 years of life but did not suppress the onset of atopic asthma (Mochizuki et al., 2017).

Genetic susceptibility to certain infections may also play a role in the development of asthma. Many of the known asthma risk alleles contribute to wheezing illnesses, and the interaction between rhinovirus wheezing illnesses and genetic variants in 17q locus increases asthma risk, suggesting a linkage between viral infections and asthma (Bisgaard et al., 2009; Çalışkan et al., 2013). A polymorphism in the *CDHR3* gene is also associated with early childhood asthma with severe exacerbations (Bønnelykke et al., 2014). The *CDHR3* gene encodes a protein which acts as a receptor for rhinovirus species C (Bochkov et al., 2015).

Childhood asthma is often associated with other allergic diseases, and IgE-mediated allergy together with viral respiratory infections increases the risk of asthma exacerbations (Rakes et al., 1999). In one study, the risk of developing asthma was significantly increased in infants with RV-C infection and IgE sensitization, but the mechanism is not fully understood (Bergroth et al., 2020). Prophylaxis with omalizumab, which binds to free IgE with high affinity, reduces

asthma exacerbations related to seasonal viral infections and the frequency of rhinovirus induced respiratory infections in children, strengthening the link between IgE sensitization, viral infections and asthma (Esquivel et al., 2017; Teach et al., 2015).

Airway microbiome research in paediatric asthma has shown that the airway microbiome may affect the development of the respiratory system, development and severity of asthma and influence the response to treatment of asthma (Shah et al., 2021). External factors such as viral and bacterial infections and antibiotics can result in changes in the microbiome. For example, changes in the nasal airway microbiota due to early exposure to antibiotics is associated with an increased risk for asthma (Toivonen et al., 2021). Whether the early manipulation of airway microbiome can reduce the risk of asthma is not yet established (Pijnenburg et al., 2022). The gut microbiome may also contribute to asthma risk and protection through a concept of gut – lung -axis (Depner et al., 2020).

2.2.3 Risk Factors of Asthma

Childhood asthma is more common in boys, but this sex difference is reversed after puberty (Dharmage et al., 2019). Parental asthma is a strong risk factor for asthma, and maternal asthma increases the risk of asthma even more, approximately three-fold (Lim et al., 2010). In a meta-analysis, maternal obesity increased the risk of childhood asthma by 2-3% with each 1 kg/m2 increase in maternal body mass index (Forno et al., 2014). Prenatal stress is also associated with childhood wheezing and asthma (Van De Loo et al., 2016). Some studies have reported an association with the maternal use of antibiotics and paracetamol and an increased risk of childhood asthma, but these studies have high heterogeneity (Castro-Rodriguez et al., 2016). Exposure to passive smoking and prenatal smoke exposure increase the risk of asthma by at least 20% (Burke et al., 2012). Of the perinatal factors, birth by caesarean section, prematurity and low birth weight are identified risk factors of childhood asthma (Castro-Rodriguez et al., 2016).

Meta-analyses regarding the use of antibiotics in early life and subsequent asthma risk have been inconclusive, but early antibiotic treatment seems to associate with an increased risk of asthma (Castro-Rodriguez et al., 2016). A recent register study reported that antibiotic treatment before the age of six months was associated with atopic dermatitis, asthma and inhaled corticosteroid use (Räty et al., 2024). In a birth-cohort study using causal mediation analysis, exposure to ≥2 antibiotic treatments during the first year of life was associated with an increased risk of developing asthma, and the effect was mediated partly by longitudinal changes in the nasal airway microbiota (Toivonen et al., 2021). Recurrent lower respiratory tract viral infections, mostly caused by RSV and RV-C, are reported as risk factors for

childhood asthma (Martinez, 2019). Indoor dampness and moulds are associated with an increased asthma risk as well (von Mutius & Smits, 2020).

Of the protective factors, day care attendance and having older siblings reduce the risk of asthma (Ball et al., 2000). There is no conclusive evidence for the protecting effect of breastfeeding, however (Castro-Rodriguez et al., 2016). The strongest protective factor seems to be living in a rural farm environment, which has given rise to the hygiene hypothesis (Von Mutius, 2016). The effect is especially notable in children at high risk of asthma, for example due to identified risk alleles in 17q locus (Loss et al., 2016).

Wheezing illnesses in early childhood and especially wheezing during rhinovirus infections are a risk factor for later childhood asthma in high-risk children (Jackson et al., 2008). The effect of rhinovirus induced wheezing applies mainly to the risk of atopic asthma, with RSV-bronchiolitis and early life rhinovirus-negative wheezing illnesses being stronger risk factors for nonatopic asthma (Lukkarinen et al., 2017). A possible interaction between the genetic risk factors in 17q locus, rhinovirus wheezing illness and the risk for childhood asthma has also been reported (Çalışkan et al., 2013). A recent study reported an association between early life metapneumovirus LRTI and later asthma and bronchial hyperreactivity (Myklebust et al., 2024). Different wheezing phenotype trajectories that take into consideration the temporality, type and frequency of wheeze can provide further insight into the development of asthma. Especially early or progressive non-infectious wheezing, persistent infectious wheezing and persistent general wheezing are associated with an increased risk of asthma (Warden et al., 2025).

2.2.3.1 Genetic Risk Factors

Genome wide association studies (GWAS) of asthma have identified several risk alleles for early childhood asthma which have then been confirmed with focused studies. The best documented of these are one risk allele in *CDHR3* gene in chromosome 7 and several risk alleles in the q arm of chromosome 17, in 17q12-21 locus, later referred to as the 17q locus (Bisgaard et al., 2009; Bønnelykke et al., 2014; Moffatt et al., 2010).

As previously mentioned, the *CDHR3* gene encodes a homonymous protein which serves as a transmembrane protein in cell adhesion and cell-cell interaction. It is mainly expressed in the epithelium of the airways. Interestingly, CDHR3 protein is also the only known receptor for RV-C (Bochkov et al., 2015). A single nucleotide polymorphism in *CDHR3* rs6967330 is associated with early childhood asthma with severe exacerbations (Bønnelykke et al., 2014). The same polymorphism increases the epithelial surface expression of CDHR3 and could therefore increase susceptibility to RV-C infections. Whether the increase in asthma risk is secondary

to an increased number and severity of infections, of especially RV-C etiology, or due to a yet unknown confounding factor is not established.

In the 17q locus, SNPs in multiple genes that have strong linkage disequilibrium (LD) between them, have been associated with an increased risk and varying severity of asthma. SNPs in gasdermin A (*GSDMA*), gasdermin B (*GSDMB*), Ikaros family zinc finger 3 (*IKZF3*), zona pellucida binding protein 2 (*ZPBP2*) and ORM1-like protein 3 (*ORMDL3*) coding genes are the best documented (Bisgaard et al., 2009; Stein et al., 2018).

In *GSDMA* gene, two risk alleles have been identified. In rs3894194, a missense variation causes a guanine to adenine replacement at location 536. Rs3894194 is an independent risk allele identified in GWAS studies (Moffatt et al., 2010). The risk allele rs3859192-T is located in the intron area of the *GSDMA* gene and leads to changes in the expression of the gene in lung tissue (Ardlie et al., 2015). The expression of GSDMA in lung cells is minimal, and the possible underlying causal mechanism on asthma risk is not known.

In *GSDMB,* several SNPs are associated with asthma risk. GWAS studies have identified rs2305480, rs11078927, rs11078928, rs2290400 and rs7216389 (Stein et al., 2018). The rs2305480 was the leading SNP found in the GABRIEL study and is associated with severe, recurrent asthma exacerbations in children (Bønnelykke et al., 2014; Moffatt et al., 2010). The rs11078927 was identified as an asthma risk SNP in a GWAS of North American population (Torgerson et al., 2011). A nearby SNP rs11078928 causes two separate splicing changes in the *GSDMB* gene reducing transcription rate, which could be of functional significance (Morrison et al., 2013). The SNP rs2290400 is located in the intron area of *GSDMB*, is associated with asthma risk and has a significant interaction with smoking (Marinho et al., 2012). Perhaps the most significant SNP in *GSDMB* is rs7216389, which is also located in the intron area. A thymine to cytosine change is associated with an early onset asthma and rhinovirus wheezing in early life (Çalışkan et al., 2013; Moffatt et al., 2007). The change affects the expression of ORMDL3 and GSDMB in lymphoid cell lines and lung tissue (Ardlie et al., 2015).

In *IKZF3* gene, two SNPs of significance have been reported. In the intron area, rs9303277 thymine to cytosine change is associated with childhood onset asthma (Stein et al., 2018). In Puerto Ricans and Latinos, rs907092 was the leading asthma risk SNP, even though the risk allele A does not alter the amino acid sequence (Stein et al., 2018; Yan et al., 2017).

ORMDL3 gene has 3 identified asthma risk alleles. Of these, rs1260332 is especially significant in Mexican and African Americans (Galanter et al., 2008). In the promoter region, SNP rs8076131 has the strongest association with the protective effect of rural and farm setting of the 17q locus (Loss et al., 2016). The rs4065275 is in intron area, and the risk allele G is associated with increased expression of

ORMDL3 (Stein et al., 2018). The intergenic rs8069176 is located close to *ORMDL3* and is the lead SNP for early onset asthma among children exposed to environmental tobacco some in early life (Blekic et al., 2013).

In *ZPBP2,* rs12936231 risk allele C is associated with an increased asthma risk and higher ORMDL3 and GSDMB expression but lower ZPBP2 expression (Verlaan et al., 2009).

The effects of these asthma risk alleles are modest, probably because of the complex nature of asthma pathogenesis and diverse asthma phenotypes and endotypes. While some of the identified asthma risk alleles, for example rs7216389 in *ORMDL3*, are also associated with viral wheezing illnesses in early life, the possible genetic-viral interaction in asthma risk is not yet established. More information on the interactions between asthma risk alleles and environmental factors such as infections is needed.

2.2.4 Clinical Presentation

Asthma is a chronic, heterogenous disease, characterized by airway inflammation, variable expiratory airflow limitation and symptoms of wheeze, shortness of breath, chest tightness and cough. The symptoms and airflow limitation usually vary over time and in intensity, with variations commonly triggered by factors such as exercise, allergen exposure, change in weather, viral respiratory infections or a combination of the above (Global Initiative for Asthma, 2024). Wheezing and shortness of breath are typically observed during the expirium. In children, wheezing sounds can sometimes be heard also during inspirium, and rattling due to excess mucus is also possible. The symptoms may be worse during the night and in the morning (Astma. Käypä hoito -suositus., 2022).

In up to half of the patients with asthma, symptoms initially commence in childhood (Simpson & Sheikh, 2010). Children present a unique set of challenges in defining and diagnosing asthma. Recurrent wheezing occurs in a large proportion of preschool children especially during viral infections, and not all wheezing indicates asthma. Diagnostic tests such as spirometry and peak expiratory flow (PEF) testing require adequate co-operation to obtain reliable results. For these reasons, deciding if a wheezing illness is an isolated event or representative of a clinical presentation of childhood asthma can be difficult (Caudri et al., 2009).

Wheeze is the most common and specific symptom associated with asthma in preschool children. Parents may describe any noisy breathing as wheezing, making clinician confirmation important for the diagnosis of asthma (Mellis, 2009). Wheezing episodes may be accompanied by cough, typically non-productive and recurrent or persistent. Especially cough during sleep, exercise or laughing or crying is associated with asthma. In infants and toddlers, crying and laughing equate with

exercise in older children. In poorly controlled asthma, young children typically abstain from strenuous play to avoid symptoms. Irritability, tiredness and mood changes can also be observed, especially in young children (Global Initiative for Asthma, 2024).

2.2.5 Diagnosis

The diagnosis of asthma in children is challenging and is based on clinical symptoms and, when applicable, pulmonary function tests. Laboratory tests such as blood tests and skin prick tests can support the diagnosis. The diagnosis of asthma should not be based solely on one symptom or abnormal test result (Gaillard et al., 2021). In small children, clinical criteria for asthma risk may be used to determine the need for treatment (Guilbert et al., 2004).

In toddlers, pulmonary function tests are usually not feasible due to the lack of sufficient co-operation, and the diagnosis of asthma is based on the risk factors and clinical symptoms. In preschoolers and older children, pulmonary function tests should be attempted. In preschoolers, oscillometry, combined with an exercise or bronchodilatation test increases the accuracy of asthma diagnosis. In school-aged children, spirometry with bronchodilatation, preferably combined with an exercise test, should be performed instead of oscillometry as it yields more accurate results (Beydon et al., 2007). PEF monitoring can be additionally performed from the age of 12 years (Gaillard et al., 2021). Exhaled nitrous oxide values can be measured to evaluate the eosinophilic inflammation of the lungs and is useful in guiding the possible treatment (Malmberg et al., 2003). Sensitization to aeroallergens should be measured with specific IgE tests (Global Initiative for Asthma, 2024).

If the suspicion of asthma is high, but diagnostic tests are not feasible, anti-inflammatory treatment may be tried. Alleviation of the symptoms during treatment is indicative of asthma and supports continuation of the treatment (Cloutier et al., 2020).

2.2.6 Treatment and Prevention

The two pillars of treatment of childhood asthma are bronchodilators to counter airway obstruction and anti-inflammatory medication to reduce the inflammation of the airways. The treatment of asthma is planned individually, based on the asthma phenotype, frequency and severity of symptoms, and possible comorbidities.

Inhaled bronchodilators relieve asthma symptoms quickly by relaxing the smooth muscle cells of the bronchi. Short-acting beta-agonists are usually used as the first line of treatment. If the need for bronchodilators is frequent or constant, long-acting beta-agonists may be used to improve symptom control. If the symptoms

persist or adverse effects limit the use of beta-agonists, muscarinic antagonists may be useful (Szefler et al., 2019).

Inhaled and peroral corticosteroids are effective in reducing the inflammation of the airways. Inhaled corticosteroids (ICS) are preferred as they have less systemic side-effects. According to asthma guidelines, ICS should be used if the need for bronchodilators is frequent (Global Initiative for Asthma, 2024). Recent ICS prescription serves therefore as a good indicator for symptomatic asthma. Montelukast, an anti-leukotriene agent, can be beneficial for reducing asthma exacerbations and improving lung function, when asthma control is suboptimal with ICS (Chauhan et al., 2017). Biological anti-inflammatory medications such as omalizumab, mepolizumab and dupilumab are effective in treatment of children with severe asthma. The indications for the use of biological medications are strict, and their use is limited to specialized centres (Morris et al., 2021).

As asthma is a heterogenous disease, no panacea for asthma prevention is likely to emerge. Rather, the prevention consists of several smaller interventions. Firstly, reintroducing protective factors such as contact with farm animals and pets could be considered (von Mutius & Smits, 2020). This approach was, in a way, demonstrated in the Finnish Allergy Programme, where changing the allergy strategy from avoidance to tolerance showed a concurrent plateauing of asthma and allergy prevalence (Haahtela et al., 2021). Indoor smoking bans have been shown to associate with reductions in emergency department visits and hospital admissions due to asthma in children (Frazer et al., 2016). Data on the effect of smoking ban on asthma prevalence are lacking, however.

Vitamin supplementations have been beneficial in preventing wheezing illnesses, but not in the prevention of asthma (von Mutius & Smits, 2020). RSV immunoprophylaxis and corticosteroid treatment during rhinovirus-induced wheezing have not been effective in asthma prevention (Koistinen et al., 2017; Scheltema et al., 2018). Even as there is a significant overlap in the immunopathophysiology of allergies and asthma, there is no conclusive evidence to support immunotherapy in the prevention of asthma (von Mutius & Smits, 2020). Probiotics during pregnancy or infancy are not effective in preventing childhood asthma or wheeze (Azad et al., 2013).

3 Aims

The nature of the associations observed between early life respiratory infections and subsequent asthma is still under investigation. Whether these associations are causal or only indicate an underlying, perhaps genetic predisposition to asthma is an important question in the prevention of asthma. The objective of this thesis is to further investigate these associations between acute respiratory infections in early childhood, their viral etiologies and the risk of subsequent childhood asthma. In addition, this thesis studies the association between known asthma risk alleles and early life respiratory infections. The specific objectives of each separate study are:

1. To investigate the association between acute respiratory infections in early childhood and subsequent risk of childhood asthma. (I)
2. To study whether gene alleles known to associate with an increased asthma risk are associated with an increased risk of early life respiratory infections. (II)
3. To investigate the association between early life ARIs of different rhinovirus species and the risk of childhood asthma at age 7 years. (III)

4 Materials and Methods

4.1 Study Design, Setting and Population

This study was based on the data and material of the Steps to the Healthy Development and Well-Being of Children (STEPS) Study. In publication II, data from the complementary VINKU and VINKU2 studies were incorporated.

STEPS Study (I-III)

In the STEPS Study, 1827 children born between January 2008 and April 2010 were recruited from an eligible birth cohort of 9936 children and are followed up until adulthood. No other selection criteria than language (Finnish or Swedish speaking parents) was applied. Background information was gathered by parent-filled structured question forms either during pregnancy or soon after birth. Follow-up questionnaires were distributed at 13, 18 and 24 months after birth. Qualified forms of The International Study of Asthma and Allergies in Childhood (ISAAC) were used to collect data on atopic and allergic conditions. Vaccination information was collected from the regional electronic patient registries.

The recruited children were followed from birth until two years of age with daily diaries of respiratory infections. Parents recorded all respiratory and other symptoms, as well as physician visits, diagnoses and treatment in the diary. The children were invited for a study clinic visit at the age of 2, 13 and 24 months. A subgroup of 923 children was recruited without selection criteria in an intensive follow-up of acute respiratory infections. These children had an additional scheduled visit to the study clinic at two months of age, when blood samples and a nasopharyngeal sample were obtained. Parents were encouraged to visit the study clinic if the child had an acute respiratory infection which they felt needed an evaluation by a physician.

The intensive follow-up group had nasal swab samples taken at each visit to the study clinic, with documentation of the current respiratory symptoms. At the first study clinic visit, parents were also trained in collecting the nasal swab samples themselves. Subsequently, on the onset of acute respiratory infection which did not require visit to the study clinic, the parents took nasal swab samples at home and

sent them to the laboratory by standard mail. For genome-wide genotyping, blood sample was acquired at a study clinic visit at the age of 2 months.

Data on emergency room visits, hospitalizations, and outpatient visits at the hospitals for acute respiratory infections (ARI) at 0-23 months of age and asthma diagnoses until 7.5 years of age were retrieved from medical records of the Hospital District of Southwest Finland. Asthma medications until 7.5 years of age were retrieved from electronic prescription registry via an electronic patient record system. All asthma diagnoses and asthma medication prescriptions were made by attending physicians (not the study physicians). The electronic prescription was introduced in Finland in 2010, and all public health care providers had implemented electronic prescription by 2014 and private health care providers by 2015. All pharmacies have been able to deliver electronic prescriptions since 2011. Electronic prescription became the main form of prescription in the beginning of 2017, and paper or phone prescriptions have been allowed only in exceptional situations.

VINKU Studies (II)

In the VINKU study (NCT00494624), as part of an efficacy trial of oral prednisolone on wheezing requiring hospitalization,131 children aged 3-35 months were enrolled in the study at the first wheezing episode between September 2000 and May 2002, as described earlier (Lehtinen et al., 2007). Children with varicella, recent exposure to varicella, recent systemic glucocorticoid treatment and any pre-existing conditions other than allergy and asthma were excluded from the study. Children with severe disease, defined as oxygen saturation below 92% despite additional oxygen and frequent salbutamol inhalations or need of treatment in intensive care unit were also excluded. A nasal swab sample for respiratory virus detection was taken at study entry and blood sample for genotyping was acquired at follow-up visit at the age of 8 years.

In the VINKU2 study (NCT00731575), 124 children aged 3-23 months born at gestational week 36 or later were enrolled during first acute wheezing episode which required hospital treatment beginning June 2007 until October 2009 (Jartti et al., 2015). In the VINKU2 study, long-term effectiveness of short course of oral prednisolone during the first rhinovirus induced severe wheezing episode was evaluated in children in a randomized controlled trial. In VINKU2, main exclusion criteria were chronic nonatopic illness, previous systemic or inhaled corticosteroid treatment, participation in another trial and need for intensive care unit treatment. A nasal swab sample for respiratory virus detection and blood sample for genotyping were taken at study entry.

4.2 Laboratory Methods

4.2.1 Respiratory Virus Detection

STEPS Study (I-III)

The nasal swabs collected during acute respiratory infections and study clinic visits were stored at -80°C before analysis. Swabs were suspended in phosphate buffered saline and nucleic acids were extracted with either NucliSense easyMag (BioMerieux, Boxtel, The Netherlands) or MagnaPure 96 (Roche, Penzberg, Germany) automated extractor. Extracted RNA was reverse transcribed and the cDNA was amplified using real-time, quantitative PCR for rhinoviruses, human enteroviruses and RSV as described earlier (Sterback et al., 2013; Toivonen et al., 2015). All specimens collected during influenza seasons were analyzed by reverse transcription PCR for influenza A and B viruses (Jokela et al., 2015). For samples collected in January 2009 or later (89% of samples), laboratory developed antigen detection tests were performed for influenza A and B viruses, parainfluenza type 1, 2, and 3 viruses, RSV, adenovirus, and human metapneumovirus (Ivaska et al., 2013).

VINKU studies (II)

In the VINKU study, nasal swabs taken at study entry were analyzed with PCR to detect rhinoviruses, RSV, enteroviruses, coronaviruses and human metapneumovirus. To detect RSV, influenza A and B viruses, parainfluenza viruses 1-3 and adenovirus, antigen detection tests and virus cultivation were used.

In the VINKU2 study, nasal swabs taken at study entry were analyzed for rhinovirus species A, B and C as well as RSV, influenza A and B, parainfluenza viruses 1-3, adenovirus, coronaviruses, enteroviruses, human bocavirus and human metapneumovirus. Both in-house and commercial PCR tests were used (Koistinen et al., 2017).

4.2.2 Rhinovirus Typing

Samples identified as rhinovirus-positive were sequenced and classified in species A, B, and C. Classification was based on sequencing of a genomic VP4/2 region after amplification with nested PCR primers. The sequences were analyzed using Basic Local Alignment Search Tool (BLAST, https://blast.ncbi.nlm.nih.gov) and species were assigned according to previously proposed principles (McIntyre et al., 2013).

4.2.3 Genome-wide Genotyping

Genome-wide genotyping was performed at Human Genomics Facility at Erasmus Medical Center in Rotterdam, the Netherlands. Genotyping was performed on the Infinium Global Screening Array. Eleven previously identified asthma risk alleles in *CDHR3* gene and in the 17q locus were selected for analyses based on previously published studies: rs6967330, rs9303277, rs3859192, rs3894194, rs2290400, rs2305480, rs11078927, rs8069176, rs7216389, rs12936231 and rs4065275 (Bisgaard et al., 2009; Bønnelykke et al., 2014; Çalışkan et al., 2013; Granell et al., 2013; Loisel et al., 2016; Loss et al., 2016; Panganiban et al., 2018; Schmiedel et al., 2016; Stein et al., 2018; Verlaan et al., 2009).

4.3 Definitions

In the STEPS Study, ARI was defined as an episode of rhinitis or cough, with or without fever or wheezing. ARIs were either documented in the symptom diary by parents, diagnosed by a physician at study clinic visit or recorded in the electronic medical records. The duration of 97.2% of ARIs was ≤ 30 days. To account for overlapping infections, the length of an ARI was limited to 30 days and longer ARIs (2.8%) were calculated as separate episodes with a maximum duration of 30 days. In Studies I and II, wheezing illnesses (bronchiolitis, recurrent wheezing, or acute exacerbation of asthma) were diagnosed by a physician based on expiratory distress, expiratory wheezing and other signs and symptoms. In Study III, wheezing illnesses was defined as symptoms of wheezing documented in the symptom diary by the parents or diagnosed by a physician (bronchiolitis, recurrent wheezing, or acute exacerbation of asthma). Recurrent wheezing was defined as two or more wheezing illnesses during the two-year follow-up time. Upper respiratory tract infection (URTI) was defined as an ARI without a recorded wheezing illness or pneumonia. Asthma was defined as a diagnosis of asthma in the medical records at age 6.5-7.5 years (age 7 years) with or without an electronic prescription of inhaled corticosteroids for asthma at the same age. All asthma diagnoses and corticosteroid prescriptions were made by non-study related physicians.

In the VINKU and VINKU2 studies (Study II), wheezing illnesses were diagnosed by a physician and were defined by expiratory distress and distinct expiratory wheezing sound. All wheezing illnesses in the VINKU studies were considered severe since all children in VINKU and 80% in VINKU2 were hospitalized, otherwise they were treated in the emergency department of the tertiary hospital.

In Study I, children who completed the follow-up on respiratory infections until at least 12 months of age were included in the analyses. In Study II, children who

completed the follow-up on respiratory infections until at least 12 months of age in the STEPS Study were included in the analyses of ARIs.

In the Study III, cases were defined as children with a physician-diagnosed asthma at age 7 years. Each case was matched with 3 control children within the cohort (no asthma during age 6.5-7.5 years) using R package Epi matching on sex, birth year (2008, 2009, 2010), and birth season (4 seasons) (Carstensen et al., 2025). Children missing nasal swabs at age 2 or 13 months, missing registry data on asthma at age 6.5-7.5 years, or with ARI follow-up of less than 12 months were excluded.

4.4 Statistical Analyses

Study I

Categorical data were compared with either $\chi 2$ test or Fisher exact test. Skewed data were compared by Mann-Whitney U test. Negative binomial distribution and log link with natural logarithm of follow-up time as an offset variable were used to analyse outcome counts while number of ARIs and associated outcomes were compared using negative binomial regression. Asthma risk at 7 years of age was analyzed with binary logistic regression analysis first unadjusted and then adjusted with background variables. P values < 0.05 were considered statistically significant. The data were analyzed using IBM SPSS Statistics software version 24 and SAS Software for Windows, version 9.4.

Study II

Associations between the risk alleles and the rate of ARIs as well as risk for both non-wheezing and wheezing ARIs were analyzed in the STEPS birth cohort using negative binomial regression with natural logarithm of the follow-up time as an offset using an additive genetic model (0 = wild type, 1 = heterozygous for risk allele, 2 = homozygous for risk allele). Negative binomial regression was used due to the overdispersion of the outcome data. The models were also adjusted for sex and the first five principal components of the genetic data. Two-tailed P-values were reported, with $p < 0.05$ considered statistically significant. The data were analyzed using IBM SPSS Statistics software version 26 and R version 4.0.4.

Study III

Associations between rhinovirus positive upper respiratory tract infections (URTI) and wheezing illnesses and asthma at age 7 years were analyzed with a conditional logistic regression analysis. Number of rhinovirus infections was used as a

continuous variable. Two-tailed P-values were reported, with $p < 0.05$ considered statistically significant. The data were analyzed using IBM SPSS Statistics software version 27 and R version 4.2.2.

4.5 Ethical Considerations

The STEPS Study was approved by the Ministry of Social Affairs and Health (STM 1575/2008, STM 1838/2009) and the Ethics Committee of the Hospital District of Southwest Finland (19.2.2008 §63, 15.4.2008 §134, 19.4.2011 §113). The parents of participating children were given written information about the study and gave their written, informed consent. The participants were informed about their right to withdraw consent to participate at any time, without reprisal or an effect on their medical care. The STEPS Study complied with the Declaration of Helsinki.

The VINKU studies were approved by the Ethics Committee of the Turku University Hospital and commenced only after obtaining written, informed consent from the guardians. Both studies complied with the Declaration of Helsinki.

5 Results

5.1 Study Population

STEPS Study (I-III)

The families of 1827 children were recruited in the STEPS Study. Of these children, 257 did not attend study visits or return the questionnaires or symptom diaries. Of the remaining 1570 children, 923 were recruited in the intensive follow-up group and 647 children were included in the regular follow-up of respiratory infections.

Participants in the STEPS Study were more often from families of married parents and higher occupational class than children in the eligible cohort. They were also more often firstborn and living in an urban area (Lagström et al., 2013). Inside the STEPS Study, children participating in the intensive follow-up group were similarly more likely to live in an urban area, come from families with higher maternal educational level, be firstborn and be less frequently exposed to parental smoking than children in the regular follow-up group. The baseline characteristics of the STEPS study children are presented in Table 1.

Table 1. Baseline characteristics of the STEPS study children.

Variable	STEPS Study (n = 1827)	Intensive follow-up (n = 923)
Female	869/1812 (48.0%)	435/923 (47.1%)
Delivery by c-section	248/1799 (13.8%)	124/923 (13.4%)
Premature (< 37 weeks)	100/1792 (5.6%)	38/918 (4.1%)
Low birth weight (< 2500 g)	74/1799 (4.1%)	25/923 (2.7%)
Small for gestational age	50/1792 (2.8%)	18/918 (2.0%)
Maternal asthma	126/1787 (7.1%)	71/922 (7.7%)
Paternal asthma	103/1693 (6.1%)	57/865 (6.6%)
Parental asthma	216/1792 (12.1%)	120/922 (13.0%)
Maternal allergy	580/1743 (33.3%)	323/891 (36.3%)
Paternal allergy	405/1693 (23.9%)	204/865 (23.6%)

Variable	STEPS Study (n = 1827)	Intensive follow-up (n = 923)
Parental allergy	795/1753 (45.4%)	416/896 (46.4%)
Older sibling(s)	857/1827 (46.9%)	376/923 (40.7%)
Maternal smoking dur. Pregnancy	198/1793 (11.0%)	94/919 (10.2%)
Parental smoking	166/1003 (16.6%)	104/635(16.4%)
Breastfed until 6 months of age	666/1131 (58.9%)	432/716 (60.3%)
In day care at 13 months of age	276/1264 (21.8)	185/784 (23.6%)
Eczema by 13 months of age	204/1213 (16.8%)	132/765 (17.5%)

VINKU Studies (II)

In the VINKU study, 293 children were recruited. Genotyping was successfully performed for 104 (35%) of the children. In the VINKU2 study, 124 children were recruited, and genotyping was successfully performed for 119 (96%) of the children. Of the 223 children included in the analyses, 67 (30%) were female and the median age during the hospitalization for wheezing was 13.5 months (interquartile range 7.5-19.0). The baseline characteristics of the VINKU and VINKU2 study children are presented in Table 2. In the earlier VINKU study, less baseline information of the children has been recorded, hence the missing information.

Table 2. Baseline characteristics of the VINKU and VINKU2 study children.

Variable	VINKU (n = 293)	VINKU2 (n = 124)	Genotyped (n =223)
Female	98 (33.4%)	40 (32.3%)	67 (30.0%)
Delivery by c-section		15/112 (13.4%)	15/112 (13.4%)
Premature (< 36 weeks)	21/265 (7.9%)	0 (0.0%)	9/216 (4.2%)
Parental asthma	63/286 (22.0%)	25 (20.2%)	44 (19.7%)
Parental allergy	144/272 (52.9%)	37/92 (40.2%)	111/212 (52.4%)
Parental smoking	121/288 (42.0%)	51 (41.1%)	99 (44.4%)
Breasted until 6 months of age		44/100 (44.0%)	44/100 (44.0%)
Older sibling(s)		79/117 (67.5%)	79/117 (67.5%)
Day care attendance at study entry		37/117 (31.6%)	37/117 (31.6%)

5.2 Acute Respiratory Infections and Asthma (I)

5.2.1 Characteristics and Prevalence of Asthma

Of the 923 children in the intensive follow-up of respiratory infections, 13 withdrew from the study. Thus, medical records and electronic prescriptions were retrieved for 910 (99%) of the children. Altogether 781 (86%) children remained in the follow-up for at least 12 months, with the median follow-up time being 24.0 months (interquartile range [IQR] 20.2-24.0).

A total of 8795 ARI episodes were recorded with a mean rate of 6.2 (95% confidence interval [CI] 6.0-6.4) episodes per child per year. Episodes of wheezing diagnosed by doctor were documented in 135 (17.3%) children, with a total of 273 episodes. Of the wheezing illnesses, 46 (16.8%) led to a hospitalization. Mean age at the first wheezing episode was 0.93 years (95% CI 0.84-1.01).

Virus diagnostics was performed for 4535 (51.6%) of the ARI episodes and 164 (60.1%) of the wheezing episodes diagnosed by doctor. Rhinovirus was detected in 2671 (58.9%) of the ARI episodes with diagnostic testing, RSV in 251 (5.5%), other virus in 223 (4.9%) and two or more viruses in 69 (1.5%) episodes. In doctor-diagnosed wheezing illnesses, rhinovirus was detected in 67 (40.9%), RSV in 42 (25.6%), other virus in 4 (2.4%) and two or more viruses in 10 (6.1%) episodes.

Diagnosis of asthma was documented in 75 (8.2%) of the 910 children at 7 years of age. A prescription for inhaled corticosteroids for asthma was documented in 70 (93.3%) of these children and a diagnosis of asthma in the hospital medical records without a current prescription for inhaled corticosteroids in five (6.7%) children. Of the children with asthma, 63 had a follow-up data of ARIs of at least 12 months during the first two years of life.

5.2.2 ARIs in Children With and Without Asthma

Children with diagnosed asthma at 7 years of age had more often cough and wheezing symptoms during ARIs, visited a physician more frequently, were more often diagnosed with otitis media and pneumonia and were prescribed with antibiotics for ARIs more often during their first years of life. The viral etiology of the ARIS at age 0-23 months did not differ between the groups. The characteristics of ARIs in children with and without asthma at age 7 years are presented in Table 3.

Table 3. Characteristics of early life ARIs in children with and without asthma at age 7 years.

	ARI in Children With Asthma (n = 800)	ARI in Children Without Asthma (n = 7995)	P
Median duration, days (IQR)	8.0 (5.0-12.0)	7.0 (4.0-12.0)	0.04
Symptoms, N (%)			
Fever	253/705 (35.9)	2268/6979 (32.5)	0.07
Cough	469/705 (66.5)	3935/6979 (56.4)	< 0.001
Wheezing	158/705 (22.4)	580/6979 (8.3)	< 0.001
Rhinorrhea	642/705 (91.1)	6448/6979 (92.4)	0.21
Physician visit, N (%)	387 (48.4)	3178 (39.7)	< 0.001
Hospitalization, N (%)	26 (3.3)	52 (0.7)	< 0.001
Diagnoses during ARI, N (%)			
OM	157 (19.6)	1249 (15.6)	0.003
WI	97 (12.1)	174 (2.2)	< 0.001
Laryngitis	19 (2.4)	125 (1.6)	0.09
Pneumonia	10 (1.3)	26 (0.3)	0.001
Antibiotic treatment, N (%)	200 (25.0)	1530 (19.1)	< 0.001
Viral etiology, N (%)			
Virus positive	269/384 (70.1)	2945/4151 (70.9)	0.71
Rhinovirus	219/384 (57.0)	2452/4151 (59.1)	0.47
RSV	23/384 (6.0)	228/4151 (5.5)	
Other virus	24/384 (6.3)	199/4151 (4.8)	
Co-detection	3/384 (0.8)	66/4151 (1.6)	

Abbreviations: ARI, acute respiratory infection; IQR, interquartile range; OM, otitis media; RSV, respiratory syncytial virus; WI, wheezing illness. Children with asthma were defined as children with current asthma at age 7 years. Children without asthma were defined as children with no current asthma at age 7 years.

5.2.3 Asthma Risk

The number of ARIs per year at age 0-23 months was associated with an increased risk of childhood asthma. Children with 9 or more ARIs per year had a significantly higher risk of asthma compared to children with <5 ARIs per year (adjusted odds ratio [OR], 7.20, 95% confidence interval [CI], 2.49-20.88, $p < 0.001$) (Figure 6).

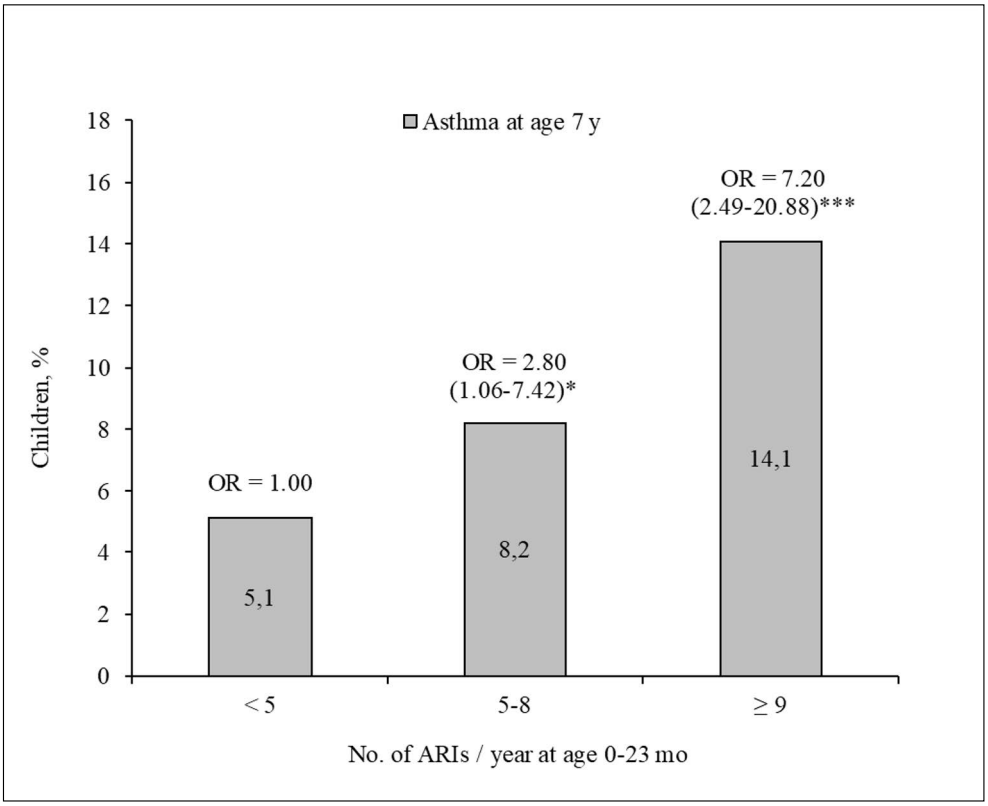

Figure 6. Prevalence of asthma at 7 years of age stratified to the number of acute respiratory infection (ARI) episodes per year at 0-23 months of age. Risk of asthma was calculated by using binomial logistic regression analysis with sex, birth by caesarean section, child's atopy at 13 months of age, parental asthma and parental smoking as covariates. Adjusted odds ratios (OR) are shown with 95% confidence intervals in parentheses. *=P < 0.05, **=P < 0.01, ***=P < 0.001.

A higher number of days with ARI symptoms per year at age 0-23 months was associated with an increased risk of asthma. Children with ARI symptoms for 60 days or more per year had a greater risk for asthma at 7 years compared to children with less than 30 days of ARI symptoms per year (OR 5.63, 95% CI 1.93 – 16.42, p < 0.01). The results are presented in Figure 7.

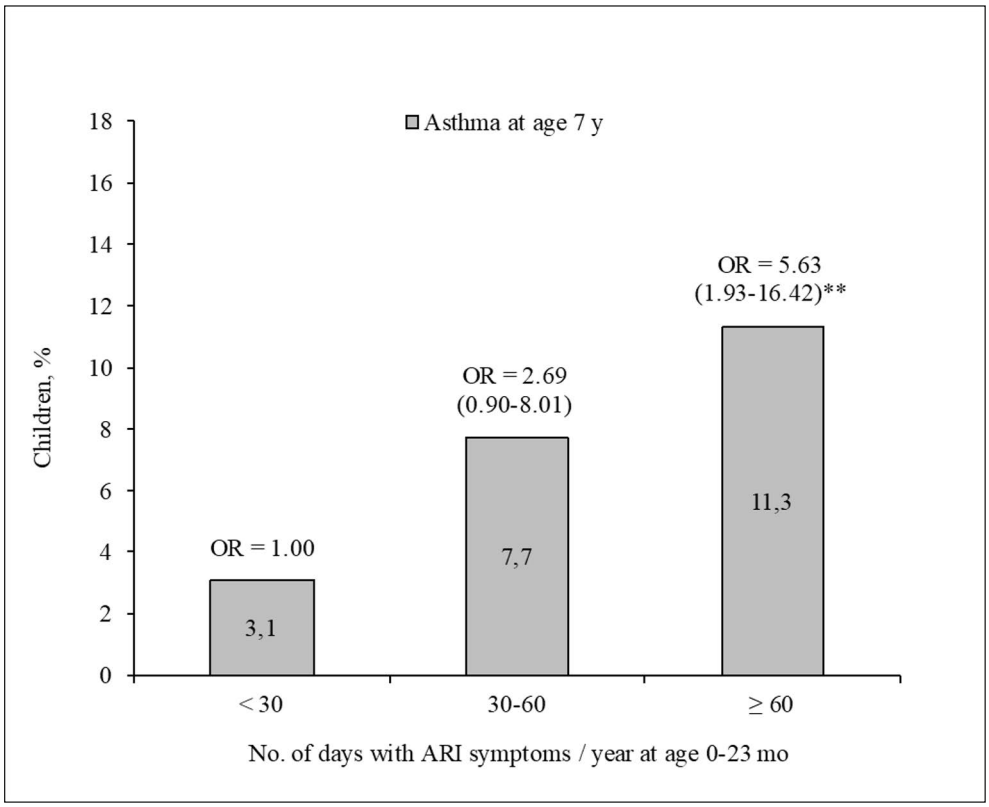

Figure 7. Prevalence of asthma at 7 years of age stratified to the number of days with ARI symptoms per year. Risk of asthma was calculated by using binomial logistic regression analysis with sex, birth by caesarean section, child's atopy at 13 months of age, parental asthma and parental smoking as covariates. Adjusted odds ratios (OR) are shown with 95% confidence intervals in parentheses. *=P < 0.05, **=P < 0.01, ***=P < 0.001.

The number of wheezing illnesses at age 0-23 months was associated with an increased asthma risk. Of the children with three or more wheezing illnesses, 45.5% had a diagnosis of asthma at age 7 years (Figure 8). Hospitalization for wheezing was associated with an increased risk of asthma at age 7 years (OR 14.93, 95% CI 4.99-44.63). Wheezing caused by rhinovirus or RSV at 0-23 months of age was associated with an increased risk of asthma (for at least 1 RSV+ wheezing episode, no rhinovirus, OR for asthma 4.90, 95% CI 1.53-15.69; for at least 1 rhinovirus+

wheezing episode, no RSV, OR 5.13, 95% CI 1.76-14.94; and for both RSV+ and rhinovirus+ wheezing episode, OR 13.93 95% CI 3.88-50.08. No wheezing used as a reference.) These results are presented in Table 2 of the original Study I. Children who developed asthma by age 7 years, had a higher rate of ARIs and more days with ARI symptoms during the first two years of their life as compared to children without asthma. They also received a significantly higher number of antibiotic treatments for ARIs during the age 0-23 months (Table 4).

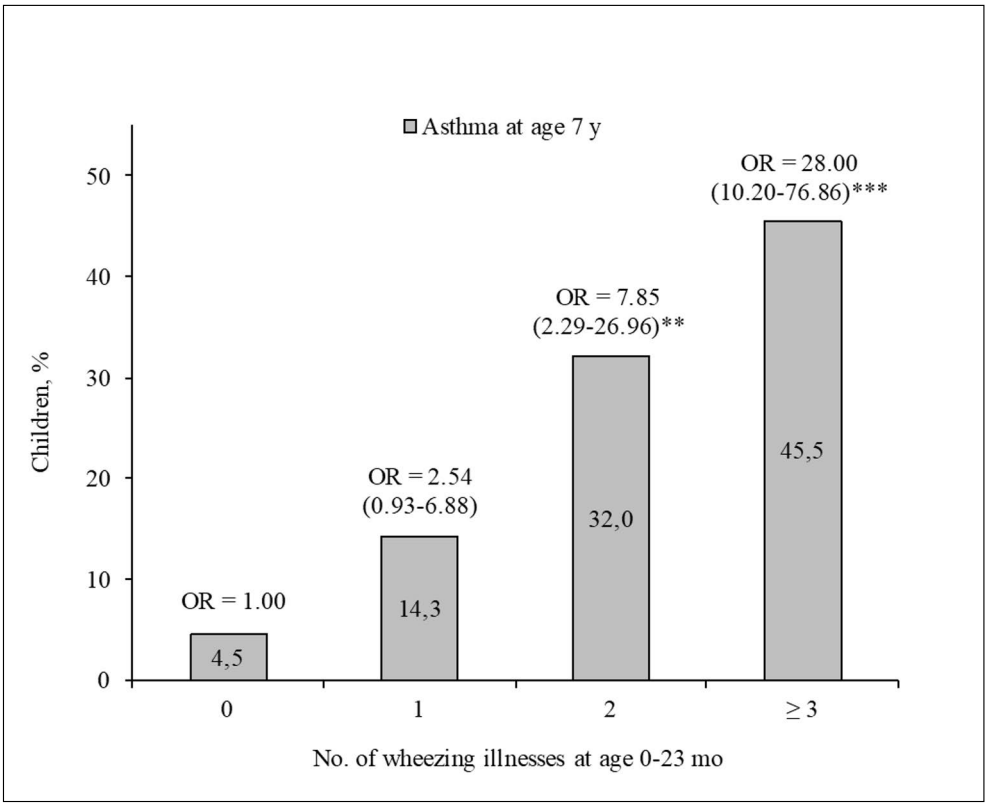

Figure 8. Prevalence of asthma at 7 years of age stratified to the number of wheezing illnesses at 0-23 months of age. Risk of asthma was calculated by using binomial logistic regression analysis with sex, birth by caesarean section, child's atopy at 13 months of age, parental asthma and parental smoking as covariates. Adjusted odds ratios (OR) are shown with 95% confidence intervals in parentheses. *=P < 0.05, **=P < 0.01, ***=P < 0.001.

Table 4. Burden of early life ARIs in children with and without asthma at age 7 years.

	Children With Asthma (n = 63)	Children Without Asthma (n = 718)	P value
No. of ARIs per year, mean (95% CI)	6.8 (6.0-7.6)	6.1 (5.9-6.3)	0.07
Days with ARI symptoms per year, mean (95% CI)	64.8 (53.4-78.7)	50.2 (47.5-53.0)	0.01
Days with wheezing per year, mean (95% CI)	5.2 (3.0-9.2)	1.6 (1.4-1.9)	< 0.001
Number of OM per year, mean (95% CI)	1.3 (1.0-1.7)	1.0 (0.9-1.0)	0.05
Antibiotic treatments for ARIs per year, mean (95% CI)	1.8 (1.4-2.4)	1.2 (1.1-1.3)	0.008

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; OM, otitis media.

5.3 Asthma Risk Alleles and Respiratory Infections (II)

5.3.1 Characteristics

Genotyping was successfully performed for 785 (85%) of the STEPS Study children. Of these children, 748 (95%) had follow-up data on wheezing illnesses and were included in the analyses of wheezing illnesses. Of the genotyped children, 694 (88%) had completed the infection follow-up for one year or more and were included in the analyses of ARIs. Genotyping was successfully performed for 104 (35%) children in VINKU and for 119 (96%) children in VINKU2 study. The lower proportion of genotyped children in the VINKU study is due to the blood samples for genotyping being collected at the 8-year follow-up visit, whereas in VINKU2 they were obtained at study entry.

A total of 247 wheezing illnesses and 7745 ARIs were documented in the STEPS children, and 4260 nasal swabs were obtained. Of the children, 128 (17%) had at least one wheezing episode and 53 (7%) had two or more wheezing episodes before the age of 2 years. The incidence of ARIs was 6.3 episodes per child-year during the first 2 years of life.

The distribution of the SNPs in the STEPS and VINKU study children is presented in Table 5. Three of the selected SNPs in *GSDMB* gene (rs2305480, rs11078927 and rs8069176) had almost identical distributions due to strong LD. Therefore, subsequent results are only presented for rs2305480, the best documented of these three SNPs.

Table 5. Distribution of SNPs in the study children (n = 971).

Gene	SNP	Number of risk alleles		
		0	1	2
CDHR3	rs6967330-A	537 (55.3%)	366 (37.7%)	68 (7.0%)
IKZF3	rs9303277-C	294 (30.3%)	484 (49.8%)	193 (19.9%)
GSMDA	rs3859192-T	271 (28.0%)	481 (49.6%)	217 (22.4%)
GSDMA	rs3894194-T	321 (33.1%)	465 (47.9%)	185 (19.1%)
GSDMB	rs2290400-A	270 (28.0%)	488 (50.5%)	208 (21.5%)
GSDMB	rs7216389-T	273 (28.1%)	489 (50.4%)	209 (21.5%)
GSDMB	rs2305480-C	261 (26.9%)	490 (50.5%)	220 (22.7%)
GSDMB	rs11078927-T	260 (26.8%)	491 (50.6%)	220 (22.7%)
GSDMB	rs8069176-A	260 (26.8%)	492 (50.7%)	219 (22.6%)
ZPBP2	rs12936231-C	285 (29.4%)	489 (50.4%)	197 (20.3%)
ORMDL3	rs4065275-G	259 (26.7%)	487 (50.2%)	225 (23.2%)

Abbreviations: *CDHR3*, cadherin-related family member 3; *GSDMA*, gasdermin A; *GSDMB*, gasdermin B; *IKZF3*, ikaros family zinc finger 3; *ORMDL3*, ORM1-like protein 3; SNP, single nucleotide polymorphisms; *ZPBP2*, zona pellucida binding protein 2.

5.3.2 Acute Respiratory Infections

The risk allele in *CDHR3* and three of the risk alleles in 17q locus were weakly associated with a higher rate of ARIs, while one risk allele (rs12936231-C) was at the limit of statistical significance (p = 0.05).

When rhinovirus infections were studied separately, the risk alleles rs6967330-A in *CDHR3* and rs3894194-T in *GSDMA* gene were associated with a higher risk for acute rhinovirus-positive respiratory infections (incidence rate ratio [IRR] 1.10, CI 1.01-1.20, p = 0.03; and IRR 1.08, 95% CI 1.00-1.17, p = 0.05 respectively). Other studied SNPs were not associated with an increased risk for rhinovirus-positive ARIs.

All the studied locus 17q alleles except for *GSDMA* rs3859192-T were associated with an increased risk of RSV-positive ARI episode. Conversely, *CDHR3* SNP rs6967330-A was associated with a lower risk of RSV-positive ARI episode (OR 0.64, 95% CI 0.48-0.84, p = 0.001). The associations between total number of ARIs and risk alleles are presented in Table 6. Results by viral etiology are presented in Table 3 of the original Study II.

5.3.3 Non-wheezing and Wheezing ARIs

When wheezing illnesses were excluded from the analysis, the risk allele rs6967330-A in *CDHR3* was associated with a higher rate of ARIs and rhinovirus-positive ARIs, but with a smaller risk for RSV-positive ARIs. SNPs in the 17q locus had no statistically significant associations with non-wheezing ARIs.

The studied SNPs in *IKZF3*, *GSDMA*, *GSDMB*, *ZPBP2* and *ORMDL3* genes were associated with a higher risk for wheezing illness of any etiology, as well as a higher risk for rhinovirus-positive and RSV-positive wheezing illness except for *GSDMB* rs2305480-C which had no association with the risk of RSV-positive wheezing illness. *CDHR3* risk allele was not associated with a risk for wheezing illness in general, or with a risk for rhinovirus-positive wheezing illness. It was associated, however, with a lower risk for RSV-positive wheezing illness (OR 0.43, 95% CI 0.22-0.85, p = 0.01).

Of the studied SNPs, *GSDMA* rs3859192-T and rs3894194-T as well as *GSDMB* rs7216389-T were associated with recurrent wheezing (for rs3859192-T, OR 1.61, 95% CI 1.07-2.40, p = 0.02).

In the VINKU studies, all asthma risk alleles were associated with a higher risk for severe wheezing illness of any etiology, and rhinovirus-positive wheezing illness, apart from *CDHR3* rs6967330-A. The results by clinical presentation are presented in Table 6. Tabulated results by viral etiology are presented in tables 4 and 6 of original Study II. In VINKU studies, all wheezing illnesses led to hospital admission and are therefore considered severe.

Table 6. Associations between asthma risk alleles and acute respiratory tract infections.

Gene	SNP	ARI episodes		Non-wheezing ARI		Wheezing illness		Recurrent wheezing		Severe wheezing (VINKU)	
		IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
CDHR3	rs6967330-A	1.06 (1.01-1.12)	0.02	1.07 (1.01-1.13)	0.02	0.93 (0.69-1.27)	0.66	1.09 (0.71-1.69)	0.70	1.01 (0.79-1.29)	0.91
IKZF3	rs9303277-C	1.05 (1.00-1.10)	0.06	1.04 (0.99-1.09)	0.16	1.56 (1.18-2.06)	0.002	1.40 (0.94-2.10)	0.10	1.65 (1.32-2.06)	< 0.001
GSMDA	rs3859192-T	1.04 (0.99-1.09)	0.16	1.02 (0.97-1.08)	0.36	1.46 (1.11-1.92)	0.006	1.61 (1.07-2.40)	0.02	1.37 (1.10-1.71)	0.005
GSDMA	rs3894194-T	1.05 (1.00-1.10)	0.04	1.04 (0.99-1.09)	0.13	1.51 (1.15-1.97)	0.003	1.59 (1.08-2.36)	0.02	1.31 (1.06-1.63)	0.01
GSDMB	rs2290400-A	1.05 (1.00-1.10)	0.05	1.04 (0.99-1.09)	0.13	1.59 (1.21-2.11)	0.001	1.50 (1.00-2.25)	0.05	1.56 (1.25-1.96)	< 0.001
GSDMB	rs2305480-C	1.05 (1.00-1.10)	0.06	1.04 (0.99-1.09)	0.15	1.40 (1.06-1.85)	0.02	1.44 (0.96-2.16)	0.08	1.48 (1.18-1.85)	0.001
GSDMB	rs7216389-T	1.05 (1.00-1.11)	0.04	1.04 (0.99-1.09)	0.11	1.57 (1.19-2.07)	0.001	1.51 (1.01-2.26)	0.05	1.59 (1.26-1.98)	< 0.001
ZPBP2	rs12936231-C	1.05 (1.00-1.10)	0.05	1.04 (0.99-1.09)	0.13	1.57 (1.19-2.07)	0.002	1.41 (0.95-2.13)	0.09	1.64 (1.31-2.45)	< 0.001
ORMDL3	rs4065275-G	1.04 (0.99-1.09)	0.14	1.03 (0.98-1.08)	0.29	1.49 (1.13-1.96)	0.005	1.39 (0.93-2.08)	0.11	1.51 (1.21-1.88)	< 0.001

Abbreviations: ARI, acute respiratory infection; *CDHR3*, cadherin-related family member 3; CI, confidence interval; *GSDMA*, gasdermin A; *GSDMB*, gasdermin B; *IKZF3*, ikaros family zinc finger 3; IRR, interquartile range; OR, odds ratio; *ORMDL3*, ORM1-like protein 3; SNP, single nucleotide polymorphisms; *ZPBP2*, zona pellucida binding protein 2.

5.4 Rhinovirus Species and Asthma Risk (III)

5.4.1 Characteristics and the Distribution of Rhinovirus Species

Of the 923 children recruited in the intensive follow-up group, 13 withdrew from the study. Registry data was available for all the remaining 910 children. Of these, 715 (77.5%) had available nasal swab samples. Children with ARI follow-up time of less than one year were then excluded. Of the remaining 631 children, 56 were diagnosed with asthma at age 7 years and were matched with 168 controls without asthma. The formation of the nested case-control study cohort is presented in figure 9.

From the 224 STEPS Study children included, a total of 1916 nasal swab samples were collected (median 6 samples per child, IQR 3-9). Of the samples, 574 were collected during routine follow-up and study clinic visits with no present symptoms of an ARI. Rhinovirus was detected in 870 (45.4%) of the samples, and of these samples, 807 (92.8%) were successfully classified into species RV-A, RV-B and RV-C based on their VP4/2 sequence. RV-A was detected in 248 samples, RV-B in 28 samples and RV-C in 531 samples.

Only the rhinovirus-positive samples collected during an ARI were included in the analyses (792 samples). Of these ARIs, 687 (86.7%) were URTIs while 105 (13.3%) were wheezing illnesses. Of the wheezing episodes, 44 were doctor-diagnosed and 61 were documented by parents in the symptom diaries. Of the wheezing episodes, 6 required hospital admission. There were no recorded RV-B positive wheezing illnesses.

Of the children, 118 (52.7%) had a wheezing episode during the follow-up period. In 83 (70.3%) of the first wheezing episodes, a viral sample was available. Of these wheezing episodes, 42 were rhinovirus-negative and 4 could not be typed due to a missing typing sample. Distribution of the typing results is presented in Table 7.

Table 7. Distribution of the rhinovirus typing results.

RV species	All samples (N = 1916)	ARI (N = 1342)	URTI (n = 1145)	Wheezing illness (n = 197)
RV-negative	1047 (54.6%)	550 (41.0%)	458 (40.0%)	92 (46.7%)
RV-positive	869 (45.4%)	792 (59.0%)	687 (60.0%)	105 (53.3%)
RV-A	248 (12.9%)	231 (17.2%)	189 (16.5%)	42 (21.3%)
RV-B	28 (1.5%)	15 (1.1%)	15 (1.3%)	0 (0.0%)
RV-C	531 (27.7%)	495 (36.9%)	442 (38.6%)	53 (26.9%)

Abbreviations: ARI, acute respiratory infection; RV, rhinovirus; URTI, upper respiratory tract infection.

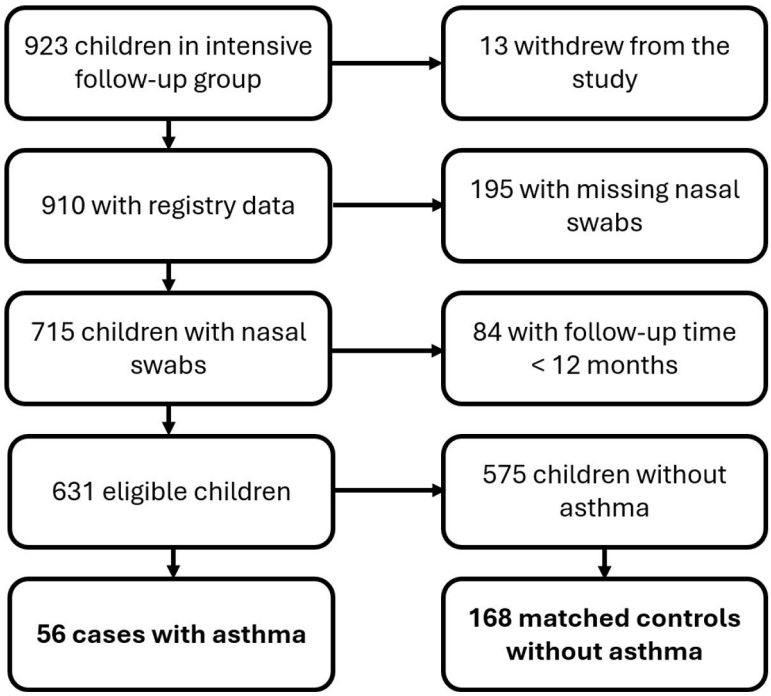

Figure 9. Formation of the case-control study cohort.

5.4.2 Rhinovirus Species in URTI and Risk of Asthma

Upper respiratory tract infections caused by RV-A, RV-B or RV-C were not associated with the risk of childhood asthma. The results are presented in Table 8a. Rhinovirus etiology of the first URTI was not associated with the risk of childhood asthma, when compared to rhinovirus-negative URTIs (Table 8b).

5.4.3 Rhinovirus-positive Wheezing Illness and Risk of Asthma

Wheezing illnesses caused by RV-A and RV-C were associated with a higher risk of childhood asthma (OR 1.80, 95% CI 1.21-2.68, p = 0.004; and OR 1.73 95% CI 1.17-2.58, p = 0.006, for each infection, respectively). The results are presented in Table 8a.

Children who had a RV-A positive sample taken during their first wheezing episode had a higher risk of childhood asthma compared to children with no wheezing illness (OR 2.93, 95% CI 1.10-7.78, p = 0.03) and the risk was not different from children with a rhinovirus-negative first wheezing illness. RV-C etiology of the

first wheezing illness was not significantly associated with a higher risk for childhood asthma. The results are presented in Table 8b.

Table 8a. Rhinovirus infection by species and clinical presentation and the risk of asthma.

URTI (n = 687)	OR (95% CI)	P value	Wheezing illness (n = 105)	OR (95%)	P value
RV-A (n = 189)	0.96 (0.73-1.26)	0.76	**RV-A (n = 42)**	**1.80 (1.21-2.68)**	**0.004**
RV-B (n = 15)	0.52 (0.13-2.13)	0.36	**RV-B (n = 0)**	N/A	
RV-C (n = 442)	0.92 (0.79-1.07)	0.29	**RV-C (n = 53)**	**1.73 (1.17-2.58)**	**0.006**

Table 8b. First Rhinovirus infection by species and clinical presentation and the risk of asthma.

First URTI (n = 687)	OR (95% CI)	P value	First wheezing illness (n = 105)	OR (95%)	P value
RV-negative (n = 50)	ref		**No wheezing (n = 106)**	ref	
			Wheezing, no detected RV (n = 77)	**1.95 (1.05-3.63)**	**0.03**
RV-A (n = 18)	2.34 (0.65-8.48)	0.20	**RV-A (n = 13)**	**2.93 (1.10-7.78)**	**0.03**
RV-B (n = 2)	1.56 (0.16-14.84)	0.70	**RV-B (n = 0)**	N/A	
RV-C (n = 50)	0.81 (0.32-2.06)	0.66	**RV-C (n = 24)**	1.79 (0.72-4.41)	0.21

Abbreviations: CI, confidence interval; OR, odds ratio; URTI, upper respiratory tract infection.

6 Discussion

6.1 Acute Respiratory Infections

In this prospective birth cohort study, children with high rates of ARIs before the age of two years had an increased risk for asthma at 7 years of age. The mean duration of ARIs were longer and the infections were more severe in children who later developed asthma compared to children without asthma. The viral etiology of the ARIs did not differ. We also documented that early wheezing illnesses caused by either RSV or rhinovirus are a strong risk factor for later asthma.

Limited earlier data are available about the association of all ARIs – including upper and lower ARIs presenting with or without wheezing – at early age and later asthma in a community-based setting. A previous study from the same birth cohort reported that children with recurrent respiratory tract infections defined as more than 98 days with ARI symptoms per year (90^{th} percentile) had an increased risk for asthma at 2 years of age (Toivonen, Karppinen, et al., 2016). These new results provide further evidence of the association of ARIs with later asthma by extending the scope until 7 years of age.

In line with these results, another Finnish prospective cohort study reported that both upper and lower respiratory tract infections in early childhood were associated with asthma at age 20-27 years (Rantala et al., 2015). The study included 2568 randomly selected children of ages 1 to 7 years, whose parents estimated the number of the child's respiratory infections during the past year. After a follow-up of 6 and 20 years, the frequency of doctor-diagnosed asthma was assessed via a questionnaire. Similarly, in a high-risk cohort in the United States, the number of respiratory infections during the first year of life was assessed by a questionnaire. High number of respiratory infections was associated with an increased risk of asthma at 7 years of age, the risk of asthma being further increased in children sensitized to mold (Perez Ramirez et al., 2018). In our study, the rigorous use of symptom diaries allowed a more precise exposure-response -analysis, which showed a clear increase in the risk of asthma as both the number of ARI episodes and the days with ARI symptoms increased. This study also broadens the generalizability of the observed association by studying a healthy birth cohort and documenting both upper and lower respiratory tract infections.

In this study, early ARIs were more severe in children with asthma at 7 years of age than in children without asthma. Absences from day care, physician visits, hospitalizations, cough, wheezing, acute otitis media, pneumonia, and antibiotic treatments were more frequent during ARIs in the first 24 months of life in children who had asthma at 7 years of age as compared to those who did not develop asthma. Although a part of this morbidity is probably caused by early wheezing illnesses, it is notable that the vast majority of ARIs in both groups of children were upper respiratory tract infections without wheezing. It seems that children who later develop asthma are more susceptible not only to wheezing but also to uncomplicated ARIs and to complications such as acute otitis media and pneumonia already during the first years of life. In concordance with our results, in a previous prospective birth cohort study with 2531 children, otitis media in infancy was associated with the risk of asthma at 4 years of age (Nafstad et al., 2000). These findings may reflect altered immunological responses to pathogens in children who develop asthma. However, the virus etiology of all ARIs at 0-23 months of age did not differ between children with and without asthma at 7 years of age, suggesting that there is no pathogen-specific immunologic weakness. This is in line with an earlier study reporting that the number of respiratory episodes in the first years of life, regardless of the viral etiology, is associated with asthma at 7 years of age (Bønnelykke et al., 2015).

Several studies have shown the association of early life lower respiratory infections with later asthma (Backman et al., 2018; Balekian et al., 2017; Lukkarinen et al., 2017; Myklebust et al., 2024), especially in sensitized children (Jackson et al., 2008; Kusel et al., 2007). In line with previous data, we found that wheezing illnesses at 0-23 months of age were associated with an increased risk for asthma at 7 years of age. In this study, as many as 83% of the wheezing illnesses were treated at outpatient clinics or in the emergency room without a need for overnight hospital stay. Recurrent doctor-diagnosed wheezing illnesses and severe wheezing illnesses leading to hospitalization at 0-23 months of age were associated with a further increase in the risk of asthma at 7 years of age. In studies of high-risk birth cohorts and hospital materials, rhinovirus associated wheezing has been an even more important risk factor for later asthma than RSV-associated wheezing, particularly in children with other risk factors for asthma (Jackson et al., 2008; Rubner et al., 2016). In this study, both rhinovirus and RSV -associated wheezing illnesses were associated with an increased risk of asthma. As in previous studies, parental asthma and child's atopy were associated with an increased risk of asthma at 7 years of age.

The findings of this study suggest common mechanisms behind susceptibility to ARIs and asthma. Airway hyper-reactivity in children who later develop asthma may contribute to prolonging symptoms during ARIs, but other immunologic explanations are also possible. Altered interferon responses to respiratory viruses in airway epithelia have been detected in children with asthma (Altman et al., 2017;

Baraldo et al., 2018). An exaggerated host response to respiratory viruses has been suggested as a risk factor for asthma and could aggravate symptoms of ARI as well. Airway microbiome and genetic susceptibility factors may also have an influence on both the severity of respiratory infections and risk of asthma (Çalışkan et al., 2013; Teo et al., 2015). The possibility of a causal relationship between early life ARIs and subsequent asthma may also be entertained. Both RSV and rhinovirus have been shown to cause acute and chronic lung changes similar to asthma and associate with prolonged airway hyperresponsiveness in animal models (Feldman et al., 2015). During infancy, changes in lung remodeling and in the trajectory of the maturing immune system may be induced by viral infections (Heinonen et al., 2019). Frequent viral respiratory infections and associated inflammatory reactions could therefore adversely affect the developing lungs.

6.2 Genetic Risk Factors

In this research, we discovered that previously recognized asthma risk alleles in *CDHR3*, *GSDMA*, and *GSDMB* were associated with an elevated rate of all ARIs. Furthermore, the risk alleles in *CDHR3* and *GSDMA* were associated with a higher rate of rhinovirus-positive ARIs, while risk alleles in *GSDMA*, *GSDMB*, *IKZF3*, *ZPBP2*, and *ORMDL3* correlated with an increased risk of RSV-positive ARIs. Additionally, when wheezing and non-wheezing ARIs were analyzed separately, the studied alleles at the 17q locus (*GSDMA*, *GSDMB*, *IKZF3*, *ZPBP2*, and *ORMDL3*) were associated with a higher risk of all wheezing illnesses and rhinovirus-positive wheezing illnesses in early childhood but showed no significant association with non-wheezing ARIs. Interestingly, in contrast to the relationship with rhinovirus infections, the risk allele in *CDHR3* was linked to a lower risk of RSV-positive ARIs.

Earlier studies have identified associations between the 17q locus alleles in *GSDMA*, *GSDMB*, *IKZF3*, *ZPBP2*, and *ORMDL3* and an increased risk and severity of childhood asthma, along with an increased incidence of early wheezing illnesses (Bønnelykke et al., 2014; Granell et al., 2013; Moffatt et al., 2007, 2010). The mechanisms behind these genetic links are not fully understood, and the functions of the genes are only partially defined (Stein et al., 2018). Gasdermin B, encoded by *GSDMB*, is involved in epithelial cell pyroptosis (Panganiban et al., 2018). The *ORMDL3* gene encodes ORMDL3, a protein that inhibits sphingolipid synthesis (Galanter et al., 2008; Moffatt et al., 2010). The asthma risk alleles in *ORMDL3* influence its expression and affect protein binding and interleukin production in both blood and nasal epithelial cells, where sphingolipid levels depend on *ORMDL3* expression (Rago et al., 2021). *IKZF3* encodes Ikaros family zinc finger protein 3, which plays a role in lymphocyte differentiation (Read et al., 2021). *ZPBP2* encodes

Zona pellucida binding protein 2, and the SNP rs12936231 in *ZPBP2* influences *ORMDL3* expression (Moffatt et al., 2007).

This study revealed that all the studied risk alleles at the 17q locus were linked to a higher risk of wheezing illnesses, both in the STEPS birth cohort and in the combined VINKU data. Additionally, the risk alleles in *GSDMA* and *GSDMB* were significantly related to recurrent wheezing illnesses in the STEPS cohort, while risk alleles in other 17q genes showed weaker, non-significant associations. These consistent findings in both an unselected birth cohort (STEPS) and children with severe wheezing illnesses (VINKU) reinforce the idea of similar underlying mechanisms in early childhood wheezing and later asthma. However, there were differences between the two studies regarding virus-specific wheezing illnesses. In the STEPS Study, all 17q risk alleles were associated with rhinovirus- and RSV-positive wheezing illnesses, but in the VINKU studies, associations were significant only for rhinovirus-positive wheezing illnesses, with weak and non-significant associations for RSV-positive wheezing. These discrepancies may be due to the small number of RSV-positive children in the VINKU studies, but differences in the study populations also need to be considered. Most wheezing illnesses in the STEPS cohort were mild, with children being managed as outpatients, whereas the VINKU studies focused on hospitalized children with severe wheezing illness. Previous birth cohort studies, which focused on children with asthma or respiratory allergies in their family history, have shown associations between 17q locus alleles and rhinovirus-positive wheezing but not with RSV-positive wheezing (Çalışkan et al., 2013).

CDHR3 encodes a transmembrane protein primarily expressed in the airway epithelium and serves as the sole identified receptor for rhinovirus species C (Bochkov et al., 2015). Previous research has indicated that allele A at rs6967330 in *CDHR3* is linked to an increased risk and severity of childhood asthma (Bønnelykke et al., 2014). In this study, the allele was not significantly associated with an increased risk of wheezing illness, rhinovirus-positive wheezing illness, or recurrent wheezing. Rhinovirus-positive wheezing illnesses and recurrent wheezing are strong predictors of later asthma, and our results suggest that the genetic risk related to the *CDHR3* variant for rhinovirus induced wheezing and subsequent rhinovirus related asthma may differ, or our study may not have had enough power to detect subtle associations.

Earlier research on children at an increased risk for asthma has shown that allele A at *CDHR3* rs6967330 is connected to a higher risk of ARIs, particularly those caused by rhinovirus species C (Bønnelykke et al., 2018). Our study adds to this knowledge by demonstrating that in a large, unselected birth cohort, this *CDHR3* allele is associated with an increased rate of all ARIs and rhinovirus-positive ARIs. This is biologically plausible since allele A at *CDHR3* rs6967330 enhances receptor binding and replication of rhinovirus species C in transfected cells (Bochkov et al.,

2015). Notably, the asthma risk allele in *CDHR3* was found to be associated with a lower risk of RSV-positive wheezing illness and RSV-positive ARIs in the STEPS cohort. This association was not confirmed nor ruled out in the VINKU studies, and as *CDHR3* is not involved in RSV pathogenesis, the underlying mechanism for this association is still unclear. Previous research has demonstrated viral interference between rhinovirus and RSV (Karppinen et al., 2016), which could explain this result.

Besides *CDHR3* rs6967330, the asthma risk alleles at the 17q locus also appeared to be associated with an increased total number of ARIs in the STEPS cohort. However, these associations were relatively weak and only significant for *GSDMA* (rs3894194) and *GSDMB* (rs2290400 and rs7216389). Interestingly, there were no significant links between 17q alleles and rhinovirus infections, with only *GSDMA* (rs3894194) showing a statistical significance. Rhinoviruses are the leading cause of ARIs in children, thus influencing the findings for all ARIs. On the other hand, we found that most asthma risk alleles at the 17q locus were significantly associated with an increased rate of RSV infections. Most RSV infections in the STEPS cohort were mild, with only 2% of children requiring hospitalization (Toivonen et al., 2020). Previous studies have assessed the genetic risk for severe hospital-treated RSV bronchiolitis, finding associations with innate immune and other genetic factors (Alvarez et al., 2018). In light of these earlier findings, our results suggest that genetic risk factors play different roles in susceptibility to mild versus severe RSV infections.

6.3 Rhinovirus Species and Asthma Risk

In the nested case-control study, carried out within the population-based birth cohort, we observed that both RV-A and RV-C wheezing illnesses before the age of 2 years were linked to an increased risk of developing asthma later in childhood. Additionally, an RV-A positive first wheezing illness was found to be associated with an increased risk of asthma. However, no rhinovirus species were found to be associated with asthma risk in URTIs. These findings are in line with Study I, which indicated that rhinovirus wheezing illnesses are linked to a higher risk of childhood asthma, whereas rhinovirus etiology of ARIs was not associated with asthma risk. This further analysis, incorporating rhinovirus genotyping, confirms that regardless of the rhinovirus species, rhinovirus-positive URTIs are not associated with asthma risk. Wheezing illnesses caused by both RV-A and RV-C are however associated with an increased asthma risk.

Wheezing illnesses are well-established predictors of childhood asthma (Kotaniemi-Syrjänen et al., 2003; Liu et al., 2017; Stein et al., 1999). Both RSV and rhinovirus-induced wheezing illnesses are linked to a higher risk of asthma later in

life, although the role of the causative virus in asthma development remains a subject of debate (Jackson & Gern, 2022; Mochizuki et al., 2017). RV-A and RV-C are more likely to cause bronchiolitis and asthma exacerbations than RV-B, which typically results in milder symptoms (Bergroth et al., 2020; Jackson & Gern, 2022; Lee et al., 2012; Turunen et al., 2016). In a previous study, both RV-A and RV-C induced bronchiolitis leading to hospitalization were found to be associated with an elevated risk of asthma, although further research in unselected populations was warranted (Bergroth et al., 2020). This study's findings suggest that while wheezing is a key risk factor for asthma, the specific pathogen responsible, including its subtype (i.e., rhinovirus species), may also influence the development of asthma. Earlier studies investigating associations between wheezing illnesses and childhood asthma have typically focused on children hospitalized due to wheezing illness (Kotaniemi-Syrjänen et al., 2003; Muñoz-Quiles et al., 2023). A strength of this study is that, within this population-based birth cohort, we were able to capture both outpatient-treated wheezing illnesses and cases that did not require healthcare intervention. Despite the milder nature of these illnesses, their clear association with asthma broadens the applicability of our findings compared to previous research.

Previous studies have demonstrated that lower respiratory infections are linked to a higher risk of asthma. A European meta-analysis involving over 150,000 children found that lower respiratory tract infections were associated with asthma in school-age children, as well as with lower forced expiratory volume in one second (FEV1) and FEV1/FEV ratios (van Meel et al., 2022). The functional differences between rhinovirus species suggest that the association between rhinovirus infections and asthma risk might vary depending on the rhinovirus species. A key distinction between the rhinovirus species lies in how they enter target cells. Most RV-B and many RV-A types use intercellular adhesion molecule 1 (ICAM-1) for entry, while RV-C interacts with CDHR3 (Basnet et al., 2019). To our knowledge, studies examining the relationship between rhinovirus species in non-wheezing infections and asthma risk have generally been retrospective and used serologic tests (Megremis et al., 2018). In this study, we found that URTIs caused by different rhinovirus species were not linked to an increased risk of asthma. This observation is noteworthy, as it suggests that the connection between rhinovirus infections and asthma risk does not follow a consistent pattern across different types of clinical presentation.

The early years of childhood are marked by rapid development of both the airway microbiome and the immune system, with complex and often bidirectional interactions. Activation of the innate immune system and remodeling of immune responses can influence the microbiome and susceptibility to pathogens, and vice versa (Di Simone et al., 2023). For instance, RV-C infections in infants hospitalized for bronchiolitis have been associated with a Moraxella-dominant microbial profile,

while RV-A is linked to Haemophilus dominance and RSV infections with Streptococcus (Toivonen, Camargo, et al., 2019). Additionally, rhinovirus infection has been reported to facilitate the acquisition and transmission of *Streptococcus pneumoniae* within families (Karppinen et al., 2017). Early-life environmental exposures can also affect the immune system's response to various allergens and pathogens. A study conducted in Wisconsin found that children living in farm environments had a lower incidence of allergic rhinitis, eczema, and severe respiratory illnesses (Ludka-Gaulke et al., 2018), and similar findings have been reported in Europe (Fuchs et al., 2012). Thus, it is plausible that the first ARIs could influence immune system development, increasing the risk of asthma. This is supported by the finding that rhinovirus as the cause of the first wheezing illness predicts atopic asthma (Lukkarinen et al., 2017). The role of the first URTIs and the rhinovirus species involved in the first wheezing illness in the development of asthma has remained unclear. This study found that the rhinovirus species responsible for the first URTI was not associated with asthma risk. Our findings were consistent with previous studies in showing that the increased risk of asthma following the first wheezing illness was influenced by the viral etiology.

Earlier studies have shown that the *CDHR3* risk allele rs7977330-A is linked to an increased risk of RV-C infections (Bønnelykke et al., 2018) and RV-C positive severe bronchiolitis is linked to earlier and prolonged use of asthma medication (Bergroth et al., 2020). Surprisingly, in this study, RV-C as the cause of the first wheezing illness was not significantly associated with asthma risk, while RV-A infections were associated with an increased risk of asthma. Furthermore, RV-C URTIs were not associated with asthma risk. The reason for this is unclear.

6.4 Strengths and Limitations

There are limitations in this study that may affect the generalizability of the results. The study children were more often first-born than those who did not participate in the study and were more often from families of a higher occupational class (Lagström et al., 2013). In addition, the follow-up time of ARIs at 0-23 months of age varied. However, we only included children with a follow-up time of at least 12 months, with 55.2% of the children completing the full follow-up time of 24 months. Since the study was conducted on Finnish children, caution should be exercised when generalizing these results to other populations.

Although daily symptom diaries completed by parents had the advantage of capturing even mild respiratory infections that did not require a doctor's visit, there were some limitations. First, the threshold for recording symptoms may have varied between families. Second, the consistency and accuracy of diary-keeping likely differed among participants. To reduce the risk of overreporting acute respiratory

infections, diagnoses were made by physicians based on the diary entries, rather than by the parents themselves. Additionally, ARIs lasting longer than 30 days were cut after 30 days into two episodes to better reflect the likelihood of consecutive infections occurring in close succession.

Parental recording of wheezing is a particular strength of this study, as it enabled the detection of wheezing episodes outside of clinical settings. However, this must be considered when interpreting the results, since parents may have included other types of respiratory sounds as wheezing in the diaries. This could have led to a slight overestimation of the number of milder wheezing illnesses.

Some limitations may also be identified specifically in the Study II. First, despite analyzing data from a large birth cohort and two large prospective studies, the groups of outpatients and hospitalized children with wheezing caused by specific viruses were relatively small, reducing the power to detect weak genetic associations. Second, we lacked data on the species distribution of rhinoviruses. Third, due to the large number of comparisons made, some findings may be coincidental. Fourth, the laboratory methods used for virus detection differed between the STEPS and VINKU studies, reflecting advancements in laboratory techniques over time. However, in both VINKU studies and in the STEPS study, PCR analysis of nasal swabs was used to detect rhinovirus and RSV, which were the primary focus of this study. Since PCR is considered the gold standard in terms of sensitivity and specificity, this difference is unlikely to have significantly affected the results.

In the Study III, the number of wheezing illnesses attributed to specific viral etiologies was limited, which reduced the power to detect weaker associations. For example, no RV-B-related wheezing illnesses were recorded.

A strength of this study is the prospective population-based birth cohort setting with unselected study population, which reduces possible selection bias. Including both outpatient and home-treated wheezing illnesses enhances the internal validity and generalizability of the findings. The intensive follow-up of ARI symptoms ensured that respiratory infections where a health care visit was not needed were also recorded. Use of register data from electronic prescriptions and hospital medical records is also a major advantage, allowing for accurate outcome identification. Retrieval of electronic prescriptions of inhaled corticosteroids allowed identification of children with symptomatic asthma, regardless of their health care provider, thus adding to the validity of the results. By electronic medical records and prescription data, 98.6 % coverage for asthma outcome was reached in the original birth cohort.

6.5 Future Implications

The findings of this dissertation have several implications for future research and public health strategies. Most importantly, the results reinforce the role of early life

respiratory tract infections as a significant risk factor for the development of asthma in children. Additionally, the identified associations between asthma risk alleles and increased susceptibility to infections give insight into the complex genetic and environmental interactions contributing to asthma pathogenesis.

Future studies should aim to evaluate the causal relationships between early viral infections and asthma. Longitudinal interventional studies could help clarify whether viral infections act as direct contributors to airway remodeling and immune dysregulation, or rather as markers of underlying predispositions. The association between genetic risk factors and infection burden highlights a need for studies that investigate whether targeted interventions, such as immunoprophylaxis or antiviral therapies, could benefit children, especially those more susceptible to asthma. Due to the widescale use of nirsevimab, this information will soon be available for RSV.

The emerging use of metabolomics and transcriptomics can help identify new endotypes of asthma, which could precede more personalized prevention and treatment strategies for asthma. A better understanding of the early markers of asthma risk could support the development of more accurate predictive tools to identify infants at high risk of asthma. The tools could combine clinical data with genetic and virological profiles to estimate asthma risk, enabling interventions such as more rigorous surveillance, lifestyle modifications or early introduction of asthma medication in high-risk individuals.

On a public health level, these results reinforce the importance of reducing the burden of viral respiratory infections in early childhood. While universal prevention of common viruses such as rhinoviruses remains a distant and perhaps unachievable vision, emerging immunoprophylactic strategies such as RSV monoclonal antibody treatment may offer indirect benefits for asthma prevention as well. Furthermore, interventions aimed at modifiable risk factors such as reducing tobacco smoke exposure and promoting microbial diversity through environmental exposure should continue.

7 Conclusions

In this study with a prospective, unselected birth-cohort, we report that a higher number of respiratory infections in early childhood was associated with an increased risk for asthma in childhood. Furthermore, certain previously identified genetic asthma risk alleles were associated with higher rates of acute respiratory infections in early childhood. We also found that both RV-A and RV-C infections with wheezing in early childhood were associated with an increased risk of asthma.

With an intensive follow-up utilizing daily symptom diaries, study clinic visits and collection of data from electronic medical records, we managed to detect that a higher number of ARI episodes and days with ARI symptoms were associated with an increased risk for asthma. The overall burden of respiratory infections was significantly greater in children who later developed asthma. The viral etiology of the ARIs did not differ between children with and without childhood asthma. The result suggests common mechanisms behind susceptibility to ARIS and asthma.

Several asthma risk alleles in 17q locus and a risk allele in *CDHR3* gene were found to be associated with a higher number of ARIs. Some of the findings were virus-specific, most notably for risk allele in CDHR3 which was associated with a higher rate of rhinovirus-positive ARIs but a lower rate of RSV-positive ARIs. When non-wheezing infections were studied separately, only the risk allele in CDHR3 had statistically significant associations with the rate of ARIs. All studied 17q risk alleles were associated with a higher risk for wheezing illnesses, however. These results suggest that the effect of genetic risk factors on susceptibility for mild and severe infections may differ. Furthermore, the effect may be pathogen specific.

In the nested case-control study (Study III), carried out within our population-based birth cohort, we also reported that acute upper respiratory infections without wheezing caused by rhinovirus species A, B, or C were not associated with risk of asthma. Both RV-A and RV-C induced early wheezing illnesses were associated with an increased risk of childhood asthma, and RV-A positive first wheezing illness was associated with an increased risk of childhood asthma in contrast with RV-C positive first wheezing illness which was not.

The findings of this dissertation emphasize the association between early life respiratory tract infections and the development of childhood asthma and highlight

the complex interplay between genetic susceptibility and environmental exposures. The observed associations between asthma risk alleles and infection burden provide further insight into the multifactorial pathogenesis of asthma, suggesting that certain children may be genetically predisposed to more frequent or severe infections that might contribute to later respiratory morbidity.

These results carry important implications for future research and public health. There is a clear need for longitudinal and interventional studies to explore causal pathways and assess whether targeted prevention strategies such as immunoprophylaxis could reduce asthma incidence in high-risk populations. Advances in transcriptomics and metabolomics may help define new asthma endotypes and improve early risk assessment, making personalized approaches to asthma prevention possible. Meanwhile, public health efforts should continue to focus on reducing early life exposure to respiratory viruses and other modifiable risk factors such as tobacco smoke, to help mitigate the burden of asthma.

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